

Natural Ionizing Radiation and Health

**Proceedings from a symposium held at
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Preface

This book is a collection of papers presented at a symposium entitled “Natural Ionizing Radiation and Health” held in Oslo June 5-6, 2001. This meeting was number 13 in a series of symposia starting in 1980 by the Committee for Geomedicine in the Norwegian Academy of Science and Letters. Since 1986 these symposia have been arranged in collaboration with the working group “Soil Science and Geomedicine” of the International Union of Soil Science. Titles of the previous symposia in this series are listed on p 6.

The present volume is dedicated to the initiator of this series of meetings, the late Professor, Dr. J. Låg, who served as a chairman of all the 12 previous symposia and editor of the “Green Books” following every meeting. Dr. Låg, born 1915, was Professor of Soil Science at the Agricultural University of Norway during the period 1949-1985. He was among the most prominent soil scientists of his generation and made significant contributions to several scientific disciplines. During his later years much of his work was devoted to the field Geomedicine, which he promoted internationally through his book with this title published by CRC Press in 1990.

Professor Låg’s achievements were a great inspiration to those of us continuing and further developing the work on geomedicine. We consider the present symposium series to be an important contribution to the future work in this area and intend to continue holding such meetings on topical issues in geomedicine. Our current definition of this field of science is the following: “*Geomedicine is the science dealing with the influence of natural environmental factors on human and animal health*”. This means that geomedicine includes the field named “Medical geology”.

This symposium would hardly have been possible without financial support from various sources. We are grateful for contributions from Geological Survey of Norway, Laborel, Norwegian Cancer Society and Norwegian Radiation Protection Authority.

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Proceedings from earlier geomedical symposia arranged by the Norwegian Academy of Science and Letters

Editor 1980-2000: *J. Låg, Agricultural University of Norway*

- 1980. Geomedical aspects in present and future research.
- 1984. Geomedical research in relation to geochemical registrations.
- 1987. Geomedical consequences of chemical composition of freshwater.
- 1987. Commercial fertilizers and geomedical problems.
- 1998. Health problems in connection with radiation from radioactive matter in fertilizers, soils and rocks.
- 1990. Excess and deficiency of trace elements in relation to human and animal health in Arctic and Subarctic regions.
- 1991. Human and animal health in relation to circulation processes of selenium and cadmium.
- 1992. Chemical climatology and geomedical problems.
- 1994. Geomedical problems related to aluminium, iron and manganese.
- 1996. Chemical data as a basis for geomedical investigations.
- 1997. Some geomedical consequences of nitrogen circulation processes
- 2000. Geomedical problems in developing countries.

The UNSCEAR 2000/2001 Reports

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Abstract

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) assesses levels and health effects of exposure to ionizing radiation. Last year the Committee published its 2000 Report. Ten scientific annexes to the Report are extensive reviews and assessments of exposures from natural background, medical and occupational radiation; radiation-associated cancer risks; DNA repair; effects at low doses; effects of radiation in combination with other agents; and an assessment of the radiological consequences of the Chernobyl accident. Recently the Committee adopted its 2001 Report on hereditary effects of radiation.

Radiation exposure has been associated with most forms of leukemia and with cancers of many organs. There is no convincing scientific evidence that cancer risk from radiation exposure disappears at very low doses. UNSCEAR estimates that lifetime cancer mortality risk after 1 Sv is about 12 % . This estimate could be reduced by 50 % for chronic exposures and low doses. The total risk of hereditary effects is 0.3-0.5 % Sv⁻¹ to the first generation following radiation. The Chernobyl accident caused severe radiation effects: 134 workers suffered from radiation sickness, 30 of whom died in the first months, and large territories were contaminated with released radionuclides. Over 1800 thyroid cancers have been reported in individuals exposed in childhood in the severely contaminated areas of Belarus, the Russian Federation and Ukraine. Apart from this increase in thyroid cancer, no radiation-associated increase in leukemia or other cancers has so far been detected.

Introduction

Man-made radionuclides are released to the environment from nuclear energy production and from uses of radionuclides in medicine, agriculture and industry. People are also exposed to radiation from medical or occupational exposures, as well as from natural sources of radiation. UNSCEAR was established in 1955 and is the body within the United Nations system with a mandate from the General Assembly to assess and report levels and health effects of exposure to ionizing radiation. UNSCEAR is the major international body, which reviews the exposure of the world population to all sources of radiation under normal

circumstances as well as after accidents. The Committee's publications form the scientific basis on which international and national agencies develop appropriate radiation protection standards for workers, patients and the general public.

Since its establishment, UNSCEAR has reported yearly to the General Assembly and submitted every few years comprehensive reports with detailed scientific annexes on the sources and biological effects of ionizing radiation. The Committee's latest assessments were published in its 2000 Reports [1]. In April 2001, the Committee adopted its 2001 Report on hereditary effects of radiation [2].

Sources of Radiation Exposure

Exposures from natural radiation are the largest component of all exposures for most people, and form the baseline upon which exposures from man-made sources are added [1]. The average annual effective dose from natural radiation is about 2.4 mSv, one third being due to external exposure and two thirds to internal exposure. Half of the total exposure comes from radon and its decay products. The level of exposure varies around the world, usually by a factor of about three, although at many locations typical levels of natural radiation exposure exceed the average levels by a factor of 10.

The use of ionizing radiation and radioactive substances causes additional radiation exposure. Some activities enhance the existing background exposure, e.g. mining. Atmospheric testing of nuclear weapons resulted in the largest release of radionuclides into the environment from man-made sources. The maximum annual dose occurred in 1963 and was on average 0.2 mSv for the world population. Since no further atmospheric test has occurred since 1980, the annual doses have decreased to small fractions of the natural radiation.

Today about 20% of the world's electrical energy is generated by nuclear fission. Nuclear installations release radioactive materials into the environment and produce radioactive waste during operation and decommissioning. The annual effective doses to individuals living in the vicinity of the installations are of the order of 0.01 mSv, although certain individuals residing near nuclear installations or nuclear test sites may be subject to higher exposures. More significant releases occur in the event of an accident. In the first year after the Chernobyl accident doses of up to 0.8 mSv were estimated in eastern and central Europe.

The use of radiation in medicine is the largest, and a growing, man-made source of exposure to ionizing radiation. The largest portion of the medical radiation exposures comes from diagnostic X-rays. Most of these occur in industrialized countries, having 25% of the world's population. There, the average annual effective dose is 1.2 mSv from all diagnostic examinations compared to 0.02 mSv or less in developing countries, the world average being 0.4 mSv. Much, and optimally most, of the effective doses from medical uses of radiation is offset by direct benefits to the examined or treated patients.

Radiation exposure also occurs as a result of occupational activities. The average annual effective doses to workers have declined over the past 20 years. At present the average dose to all workers exposed to man-made sources is 0.6 mSv per year, with 1.8 mSv to monitored

workers in the nuclear fuel cycle installations, 0.5 mSv to workers involved with other industrial uses of radiation and 0.3 mSv to medical staff. The doses to workers exposed to natural sources of radiation have been less thoroughly studied, and are on average 1.8 mSv. The average annual doses are 0.7 mSv to coal miners, 2.7 mSv to other miners and 3 mSv to aircrew. Further attention needs to be given to the evaluation of occupational exposures arising from natural sources.

Health Effects

Information on the biological effects of radiation exposure comes from studies of humans (epidemiology), studies of animals and plants (experimental radiobiology) and studies of cells (cellular and molecular biology). The key to understanding the health effects of radiation is the interaction between these sources of information [1,2].

Damage to DNA in the nucleus is the main initiating event by which radiation causes long-term damage to organs and tissues of the body. Double-strand breaks in DNA are regarded as the most likely candidate for causing critical damage. Single radiation tracks have the potential to cause double-strand breaks and in the absence of 100% efficient repair could result in long-term damage, even at low doses. Damage to other cellular components (epigenetic changes) may influence the functioning of the cell and progression to the malignant state.

Proto-oncogenes and tumour-suppressor genes control a complex array of biochemical pathways involved in interaction, growth, mitogenesis, apoptosis, genomic stability, and differentiation. Mutation of these genes can compromise these controls and contribute to the multi-stage development of cancer. Much knowledge about the multi-stage nature of carcinogenesis remains to be learned. Although the concept of sequential, interacting gene mutations as the driving force for neoplasia is established, there is a lack of understanding of the interplay between these events and the consequences for cellular behaviour. Uncertainty also exists about the contribution made to malignant development of epigenetic events.

The judgement as to whether there might be a threshold level of exposure below which biological response does not occur can be guided by mechanistic considerations. Such a threshold could occur only if repair processes were totally effective in that dose range or if a single track were unable to produce an effect. The absence of consistent indications of significant departures from linearity of carcinogenic response at low doses in cellular endpoints (chromosome aberrations, gene mutation, cell transformation), the activity of well characterized error-prone DNA repair pathways, and the evidence on spontaneous double-strand breaks in mammalian cells argue against processes that might provide for a dose threshold for radiation effects.

Radiation-associated cancer in humans is studied in exposed populations, such that excess cancers may be identified. These populations include survivors of the atomic bombings, medically irradiated patients, those occupationally exposed, individuals exposed to radionuclides released into the environment, and some people exposed to elevated levels of natural background radiation. Since the Committee's assessment of the risks of radiation-

induced cancer in the UNSCEAR 1994 Report [3], additional important information has become available from epidemiological studies.

Radiation can cause cancer in almost any tissue or organ in the body, although some sites are much more vulnerable than others. A clearer understanding of physiological modifying factors, such as sex and age, has developed over the last few years. Although differences in the absolute risk of tumour induction with sex are not large and vary with site, for most solid cancers the absolute risk is higher in women than in men. People who were young at the time of radiation exposure, have higher relative and absolute risks than older people, but again this varies by site. Further follow-up of radiation-exposed cohorts has demonstrated that excess cancers continue to occur long time after radiation exposure, and therefore, great uncertainties exist in the projection of lifetime risks.

The Life Span Study cohort of the A-bomb survivors in Japan continues to be a primary source of epidemiological data on radiation effects, including some 86,500 individuals of both sexes and all the full span of ages with data for a wide range of doses. The results of this study provide the primary basis for estimating the risk of radiation-induced cancer. Among 86,500 individuals in the Life Span Study of the survivors, there were more than 7,578 deaths from solid tumours during 1950-1990. Of these, 334 can be attributed to radiation exposure. In the same period, 87 out of 249 leukaemia deaths can be attributed to radiation exposure. This means that about 5% of the cancer deaths can be linked to radiation.

The cancer incidence and mortality data are broadly similar, both demonstrating statistically significant effects for all solid cancers combined, as well as for cancers of the stomach, colon, liver, lung, breast, ovary and bladder individually. The incidence data also provide evidence of radiation risks for thyroid cancer and non-melanoma skin cancers. Statistically significant risks have not been observed for cancers of the rectum, gallbladder, pancreas, larynx, uterine cervix, uterine corpus, prostate, kidney or renal pelvis. Associations with radiation exposure are noted for several types of leukaemia, but not for lymphoma or multiple myeloma. The numbers of solid tumours associated with radiation exposure are not sufficient to permit detailed analysis of the dose-response relationship for specific sites or types of cancer. For all solid tumours together the slope of the dose-response curve is linear up to about 3 Sv, but the dose-response curve for leukaemia is best described by a linear-quadratic function. Statistically significant risks for cancer in the Life Span Study are seen at organ doses above about 100 mSv.

Data for the Japanese A-bomb survivors are consistent with a linear or linear-quadratic dose response over a wide range of doses, but quantifying risks at low doses are less certain because of limited statistical precision or other methodological problems. Longer follow-up of cohorts with a wide range of doses will provide more essential information at low doses, but epidemiology alone cannot resolve the issue of whether or not there are low dose thresholds. However, the inability to detect increased risks at very low doses does not indicate that they do not exist.

Studies of populations exposed to medical, occupational or environmental radiation provide information on issues that cannot be addressed by the atomic bomb survivor data, such as the effects of chronic low doses or high-LET radiation, highly fractionated doses, and variability among populations. For some cancer sites, including leukaemia, breast, thyroid,

bone and liver, very useful results come from investigations other than the Life Span Study. Risk estimates derived from those studies generally agree well with those from the Life Span Study.

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

Based on the available epidemiological data, the Committee has derived risk estimates for radiation-induced cancer. For a population of all ages and both genders with an acute dose of 1 Sv (low-LET), the Committee estimates the lifetime risk for solid cancer mortality at about 12%. This estimate could be reduced by 50% for chronic exposures. Cancer incidence risks can be taken as being roughly twice those for mortality. Risks estimates for individuals being exposed as children might be twice the estimates for a population exposed at all ages. The experience of the Japanese atomic bomb survivors provides compelling evidence for linearity in estimating excess risks of solid cancers; therefore, as a first approximation, linear extrapolation of the estimates at 1 Sv could be used for estimating solid cancer risks at lower doses. This new risk estimate is similar to that published in the UNSCEAR 1994 Report [3].

Radiation exposure has also the potential for causing hereditary effects in the offspring of people exposed to radiation. Such effects were once thought to threaten the future of the human race by increasing the rate of natural mutation. However, hereditary effects have yet to be detected in human populations exposed to radiation, although they are known to occur in other species. This year the Committee adopted its 2001 Report with an annex specifically dedicated to an assessment of the hereditary effects of radiation exposure. The Committee estimates the total risk of hereditary effects at 0.3-0.5% Sv⁻¹ to the first generation following radiation, or less than one tenth of the risk of fatal carcinogenesis following irradiation.

The Chernobyl accident

The accident at the Chernobyl nuclear power plant in 1986 is the most serious accident involving exposure to ionizing radiation. The accident caused many severe effects: 134 workers suffered from radiation sickness, 28 died in the first three months and another two

soon afterwards. Large territories were contaminated, and deposition of released radionuclides was measurable in many countries of the Northern Hemisphere. A majority of the epidemiological studies completed to date are descriptive. Individual dosimetry is not available, and it is difficult to determine whether or not suspected effects are radiation-related. Reliable estimates of cancer risks can, consequently, not be given. The reconstruction of individual doses is therefore crucial for future research.

A total of 1800 thyroid cancers have been reported in individuals exposed in childhood in the severely contaminated areas of Belorussia, the Russian Federation and Ukraine. If the current trend continues, many more cases may occur in future decades, especially in individuals who were exposed at young ages. Notwithstanding problems associated with screening, these cancers were most likely caused by radiation exposures at the time of the accident. Apart from this increase in thyroid cancer, no increase in leukemia or other cancers has been detected. However, the accident caused serious social and psychological disruptions in the lives of those affected, but there has been no increase of non-malignant disorders that can be directly related to the radiation. Although the most highly exposed individuals are at an increased risk of radiation-associated effects, the great majority of the population is not likely to experience serious health consequences of radiation from the Chernobyl accident.

There is a tendency to attribute increases in the rates of all cancers to the Chernobyl accident. However, increased rates were also observed before the accident. Moreover, a general increase in mortality has been reported in recent years in most areas of the former USSR, and this must be taken into account when interpreting the results of the Chernobyl-related studies.

The Chernobyl accident might shed light on the late effects of protracted exposure, but given the low doses received by the majority of exposed individuals, any increase in cancer incidence or mortality will be difficult to detect in epidemiological studies. Many health problems other than cancer have been noted in the populations, but they are less likely to be related to radiation exposure. From a scientific point of view, there is a need to evaluate and understand the technical causes and health effects of the accident. From a human point of view, there is also an obligation to provide an objective analysis of the health consequences of the accident.

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International Commission on Radiological Protection (ICRP): On Risks and Actions

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Abstract

ICRP is a charity offering recommendations and advice on radiological protection. ICRP regards the linear, no-threshold dose response model as the currently most credible approximation of the unknown true dose response relationship for low doses and dose rates. This puts ICRP in an intermediate position in terms of predicted risk. Its current three-tier system of protection, justification-optimisation-limits, emphasises optimisation for the collective good before individual dose limitation. Thus, utilitarian criteria are given more weight than egalitarian ones. The next set of fundamental ICRP recommendations is likely to appear sometime around 2005. ICRP has proposed a shift of emphasis towards egalitarian limitation of doses, including a somewhat less anthropocentric view of protection of the environment than earlier, and the proposal was distributed for world-wide consultation by the International Radiation Protection Association, IRPA. Updated and more detailed ideas are being developed on the basis of the consultation results. These will be circulated through IRPA before final adoption of the new recommendations

Introduction

The International Commission on Radiological Protection, ICRP, was established in 1928 by the International Society of Radiology. Its mission is, according to its Constitution, to advance for the public benefit the science of radiological protection, in particular by providing recommendations and guidance on all aspects of protection against ionizing radiation. These recommendations are published in the Commission's journal, *Annals of the ICRP*.

The Commission aims at providing an appropriate standard of protection for man, without unduly limiting the beneficial practices giving rise to radiation (ICRP, 1991). Medical uses of

radiation of course provide excellent examples of this inherent dualism in radiological protection.

The Commission has four standing Committees on (1) radiation effects; (2) doses from radiation exposure; (3) protection in medicine; and (4) application of ICRP recommendations. New ICRP documents are drafted by Task Groups and Working Parties and reviewed by the Committees before approval by the Commission.

Radiation risk components: Doses

For basic dose statistics and assessments of biological and medical effects of radiation, ICRP primarily draws on the recurrent reports of the United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR.

Volume I of their most recent report (UNSCEAR, 2000a) indicates average annual doses of radiation as summarised in Table 1. The Table illuminates two facts that are often not appreciated by the layman: (a), natural sources constitute the dominating cause of exposures to radiation; and (b), the biggest man-made source is medical use of radiation.

UNSCEAR (1993) estimated that the average annual effective dose per caput from radiotherapy (i.e. the dose due to scatter radiation outside the target area) was 0.3 mSv). No estimate of the average dose due to radiotherapy was included in the 2000 UNSCEAR report. The distribution of such doses in the population is bimodal with no dose to most people but several hundred mSv to patients undergoing radiotherapy.

Radiation risk components: Effects

Basically, radiation effects comprise (1) deterministic effects (such as severe burns) that occur with certainty after doses high enough to cause major cell killing, and (2) stochastic effects that are considered to occur more or less in proportion to dose at all dose levels. In embryos and fetuses, the effect pattern reflects the special conditions during pregnancy. Mental retardation is one of the effects observed after high fetal doses.

The exact nature and shape of the dose-response relationship for stochastic effects are often discussed. UNSCEAR (2000b) notes that stochastic effects are initiated primarily as a multi-stage sequence of damage to DNA. Low dose radiation is a minor competing contributor to such damage. Much of the damage is single-strand breaks that are effectively repaired, but radiation also induces double-strand breaks, the repair of which is error-prone.

Because of this, at the cellular level the initial induction of damage due to low doses of radiation is almost certainly proportional to the dose, with no threshold. Direct observations of cellular or animal systems usually indicate an apparent linear or linear-quadratic dose response, but statistical limitations often preclude firm conclusions at levels of dose below about 100 mSv. A few studies appear to provide significant information at such dose levels, but their conflicting results indicate that the systems are complex and heterogeneous.

Table 1. Average annual effective doses per caput

Source	Dose (mSv/year)
Natural background	2.4
Diagnostic medicine	0.4 (0.02 – 1.2) 1
Atmospheric weapons testing	0.005
Chernobyl accident	0.001
Nuclear fuel cycle	0.0001
Occupational exposure	0.001 (1.3) 2

1 Global value (least developed countries – highly industrialised countries)

2 Global value (worker average)

UNSCEAR (2000b) concludes that a risk of tumour induction proportional to the dose remains the most plausible approximation of low-dose response. Epidemiological evidence indicates that the risk of fatal solid cancers at high doses is about 11% per Sv (9% for men, 13% for women, confidence interval about 5-20%). The risk at low dose is estimated to be about half of this value (confidence interval about 2-10%). Leukaemias show a linear-quadratic dose response with a risk of 1% at 1 Sv, 0.05% at 0.1 Sv. The ICRP (1991) estimates of the risk of fatal cancer (4% per Sv for occupationally exposed persons and 5% per Sv for members of the public) are similar to these numbers.

UNSCEAR (2000b) discusses modifying factors such as apoptosis and immune surveillance, and concludes that such factors may affect the rate of cancer, but do not cause any threshold. Hormesis is sometimes claimed to be a reason not to bother about radiation protection at low doses. ICRP regards hormesis as a transient response occurring at doses that ICRP considers as being of no practical relevance for protection purposes. Genomic instability provides increasing insight into the mechanism of cancer induction, and therefore indirectly into prevention and curing, but does not reflect additional new risks.

The UNSCEAR (2000b) report also discusses problems with so-called ecological correlation studies in epidemiology, and concludes that such studies are open to so serious bias by confounding factors that they cannot be used to estimate radiation risk. Furthermore, the report points out that many childhood thyroid cancers in the wake of the Chernobyl accident are obviously radiation induced, but states that the exact mechanisms and levels of risk are still poorly understood.

The current principles of protection

Since no dose is regarded as safe, dose limits cannot delineate dangerous from safe and are not efficient as tools to minimise radiation risks. Instead, ICRP has devised a three-tier system of radiation protection:

Justification of the practice or intervention at hand - No additional dose should be tolerated unless there is an associated benefit that outweighs the risk.

Optimisation of protection - Doses are to be kept *as low as reasonably achievable*; i.e. usually far below the dose limits.

Limitation of doses – Dose limits are primarily needed to ensure equitable distribution of risk, and may be useful as a regulatory instrument.

Many additional aspects and complications should be considered. These include the exposure conditions (practice or intervention), the source of exposure (public, occupational, medical), and the probability of incurring an exposure (near-certain or potential, with human factors as an important component of safety considerations).

The principles of justification and optimisation aim at doing more good than harm and at maximising the margin of good over harm. Thus, they satisfy the conditions of utilitarian ethics, in that actions are judged by their consequences. The aim of dose limitation is to ensure that no individual is exposed to undue harm. This is a case of deontological ethics, according to which some duties are imperative

Activities of ICRP

ICRP Committee 1 on radiation effects considers the risk of induction of cancer and heritable disease (stochastic effects) together with the underlying mechanisms of radiation action. The Committee also considers the risks, severity, and mechanism of induction of tissue/organ damage and developmental effects (deterministic effects). It has three current Task Groups on (1) epidemiology and dose response at low doses; (2) radiation effects on the embryo and fetus; and (3) evaluation of relative biological efficiency (RBE) for deterministic and stochastic effects.

ICRP Committee 2 on doses from radiation exposure is concerned with the development of dose coefficients for the assessment of internal and external radiation exposure. This Committee also develops reference biokinetic and dosimetric models and reference data for workers and members of the public. It has some five Task Groups, interacting in a complex fashion to achieve a further revision of the publication on 'Reference Man', a revision of the alimentary (gastrointestinal) tract model, a technical reference document on the use of the lung model in ICRP *Publication 66* (1994), anatomically more realistic phantoms, dose calculations for new reference phantoms, and further revision of internal dose coefficients and addition of external dose coefficients. ICRP Committees 1 and 2 are jointly reviewing radon

dosimetry in order to resolve the difference between dosimetric and epidemiological approaches.

ICRP Committee 3 on protection in medicine is concerned with protection of persons and unborn children when ionising radiation is used for medical diagnosis, therapy, or biomedical research. This Committee is also concerned with assessment of the medical consequences of accidental exposures. It has recently produced reports on interventional radiology, on safety in radiotherapy, and on computed tomography. Its standing Task Group on radiopharmaceuticals continuously adds new information to the web site of ICRP. The Committee has just started a Task Group on the release of nuclear medicine patients from designated clinics.

ICRP Committee 4 on the application of ICRP recommendations provides advice on the application of the recommended system of protection in all its facets for occupational and public exposure. It also acts as the major point of contact with other international organisations and professional societies concerned with protection against ionising radiation. This Committee, having just concluded its work on ICRP *Publications 81* and *82* on solid waste disposal and on prolonged exposures, is now launching three Task Groups on (1) characterising individual members of the public for radiological protection purposes; (2) optimisation and ‘stakeholder’ involvement; and (3) radiological protection in space flight.

The recent activities in ICRP Committee 3 merit some extra words. World-wide, collective doses to patients from diagnostic and therapeutic procedures are increasing. Much of the increase observed is clearly justified on clinical grounds, particularly in developing countries.

However, there are also some problems. Indiscriminate referral, where patients are subjected to examinations (or, more rarely, treatments) that are not clinically required, lead to increased collective doses due to exposure of too many persons. The other major class of problems comprises unnecessarily high doses per procedure. Non-optimised equipment or methods will of course generate such unnecessary doses, and inadequate or insufficient training of staff will aggravate the problems.

Earlier ICRP guidance concerning medical radiation described above could be classified as dealing with the system, the installation, the equipment, and the various groups of patients or other persons exposed to radiation. This logical organisation of the material works for most current users of ICRP reports, but it may also be useful to provide specific guidance on topical problems, cutting information in another direction. Such problem-oriented guidance may be particularly relevant for medical staff directly involved in the care of patients as well as for health physicists and engineers ‘at the shop floor’ in hospitals and clinics.

Future Recommendations of ICRP

The present general recommendations of ICRP (ICRP, 1991) were adopted in 1990. Traditionally, such recommendations are revised every 15 years or so. Accordingly, ICRP plans to issue recapitulated and/or consolidated new recommendations around 2005.

Some of the problems involved are mentioned below.

Firstly, all dose limits for the public are not very helpful. They refer to a sum of contributions from many sources, but not all sources and not necessarily the most important ones. Collective dose can also be problematic. This is not so much due to ICRP or the concept itself, but to misuse in that some people stretch the concept far beyond what is sensible. ICRP feels that the unlimited aggregation of collective dose over time and space into a single value is unhelpful. This should not be misconstrued; collective doses should not be ignored on the sole ground that individual doses are small. However, information must be provided fairly, and this means that the presentation of collective dose contributed by wide ranges of individual dose should be separated into blocks of limited ranges of dose and time.

Secondly, ICRP recommendations are logical but overwhelmingly complex.

Thirdly, there is an increasing awareness that radiological protection of the environment may need to be considered in its own right, not only insofar as man is concerned because radiation is transported through the environment. ICRP (1990) claimed that the standard of environmental control needed to protect man to the degree currently thought desirable will ensure that other species are not put at risk, and that individual members of non-human species might be harmed, but not to the extent of endangering whole species.

As it stands, this statement is no more than an unsubstantiated declaration of a belief. Actually, the statement is probably correct in most cases, and proper attention to the environment is unlikely to change existing discharge authorisations. But ICRP needs a comprehensive system, one that is in line with control of other pollutants, which is transparent, and with proper scientific references. ICRP recently launched a Task Group on this problem, directly under the Main Commission. The Task Group will presumably refer frequently to the 1992 Rio Declaration on sustainable development, and perhaps at the end of the day ICRP will be turning its statement upside down, saying that the standard of control needed to protect the environment will ensure that man is not put at risk.

Taking all of these problems into account, ICRP is collaborating with the International Radiation Protection Association (IRPA) to ensure a comprehensive discussion among peers all over the world of possible basic concepts for the new recommendations (Clarke, 1999). Some features of the original 'Controllable Dose' proposal follow:

- A Controllable Dose is defined as the dose, or the sum of doses, to an individual from a particular source that can reasonably be controlled by whatever means.
- The significance of a Controllable Dose would be judged by its magnitude, the benefit to the exposed person, and the ease of reducing or preventing the dose. In principle, similar actions would be attempted for doses of similar size, no matter what the source. (This in fact resembles the current system in many ways, but the advice would be organised much more transparently).
- Protection would be focused on the individual rather than the collective (the number exposed in 'critical groups' would still be an issue, and workforce doses would need to be treated much the same way as today to preclude 'dilution' of doses).
- Significantly higher doses than some tens of mSv would only be sustained in accidents and life-saving medical procedures.
- The intentional delivery of high doses in medicine, as in radiotherapy and at least some interventional procedures, would be outside the scope of 'Controllable Dose'.

In contrast to the current scheme of justification - optimisation - limitation, the proposed system would focus on individual limitation, followed by optimisation of protection against the resulting doses. It would be emphasised that justification is a societal / political exercise involving more than just health physics.

The consultation on these ideas indicated wide-spread support for the aims of the proposal, but, of course, many comments on how these aims would be achieved. ICRP is now developing more detailed proposals, taking all of the IRPA comments into account. A progress report recently appeared (ICRP, 2001). In due course, ICRP will again consult the scientific community with more specific proposals for new recommendations.

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Application of Airborne Radiometric Surveys in the Mapping of Areas with High Natural or Anthropogenic Ionizing Radiation

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Abstract

This paper presents results of an airborne gamma-ray survey over a uranium-mining district in Southeast Germany. The AERA project (Assessment of Environmental Risks by Airborne Geophysical Techniques validated by geophysical field measurements) was conducted as a part of an EC funded environmental research project in the 4th framework programme. The Geological Survey of Finland conducted the airborne measurements with three different geophysical methods in August-September 1999. The results show that the gamma-ray method mapped effectively the environmental impacts of uranium mining. Radiometric data revealed new information of known contaminated sites, but also indicated previously unknown contaminations. Areas that show increased radiation caused by e.g. uranium mining, transport and processing are presented on thematic maps. The increased uranium concentrations and the background levels are validated and calibrated by soil sampling.

Introduction

The AERA project is a pioneer project that combines airborne multisensor surveys to assess environmental risks, which are later followed up by geophysical ground checks at selected sites. The Geological Survey of Finland (GTK) coordinated the project. The GTK multisensor technique includes simultaneous measurements with magnetic, gamma ray and dual frequency electromagnetic systems. The GTK has 50 years of experience in aerogeophysical geological mapping and ore prospecting and has now applied this knowledge for the first time to survey environmental contaminations. The test site of the AERA project is located in Zwickau in Saxony, Southeast Germany. The survey area was selected because heavy mining and industrial activities have taken place in the region over the last centuries. Some of these activities have caused considerable environmental impacts, all of which are well examined and

documented. The environmental impacts comprise uranium, black coal and nickel mining as well as industrial and military activities including deposition of various types of waste.

Uranium mining in Eastern Germany

Right after World War II, the Soviet Union started exploration and mining of uranium in the Ore Mountains in Saxony and Thuringia. East Germany soon became the third largest uranium producer in the world; a total amount of 231 000 t of uranium was produced during 1946-1991. The mining was conducted both underground and in open pits. The ventilation of the mines often resulted in atmospheric transport of radon and other contaminants to residential and agricultural areas. Pumped groundwater from the mines was often released directly to rivers and creeks. According to Diehl (2000) the sediments of the rivers in the Ronneburg area show concentrations of uranium and radium over natural background values. The region has a thousand year long history of mining activities. Many old mines and tunnels provide pathways for radon transport from bedrock to residential areas.

The decommissioning comprises refilling of the open pits with waste rock from the surrounding stockpiles. The underground mines are also decommissioned and flooded. The uranium ore was processed mainly in two plants, one in Zwickau and one in Ronneburg. The tailings were deposited in large ponds close to the plants. The remediation of the tailing ponds comprises dehydrating and covering with geo-textiles and clean soil. The seepage waters are collected and treated.

Airborne gamma-ray measurements

Gamma-ray measurements have primarily been developed for uranium exploration purposes. Nowadays the method is mainly applied for geological mapping and exploration of other types of economic minerals. Gamma-ray measurements may also be applied in environmental monitoring such as mapping of radioactive contamination from fallout of nuclear accidents and plumes from power plants (Grasty, 1998). Such measurements indicate variations in the radioactivity of 0.5-1.0 metres thick surface layers of the earth. The results are presented as total radiation and equivalent concentrations of uranium, thorium and potassium. It is also possible to determine the amount of anthropogenic radioactivity from the radiation spectrum (Grasty & Multala, 1991).

The measurements were conducted with a Cessna Caravan I aircraft. The radiation measuring equipment is a gamma-ray spectrometer that consists of 5 NaI crystals. The crystal package installed in the Cessna Caravan has a total volume of 20.5 litres, the spectrometer

records 256 channels of spectral data in the range of 0.01-3.0 MeV. Three additional windows record gamma rays of K^{40} , Bi^{214} from the uranium decay series and Tl^{208} from the thorium decay series. The overall radioactivity level is recorded with a total count window. The registrations are done once per second, which leads to a sampling distance of 50-60 m at a flying speed of 180 km/h. The flying altitude in this project was 100 feet.

Results of the airborne the gamma-ray survey

Results of the gamma-ray measurements are plotted as maps of total radiation as well as concentrations of uranium, thorium and potassium. The total count and uranium maps show the impacts of uranium mining. The uranium map in Figure 1 indicates the uranium waste deposits (stockpiles in Ronneburg and Schlema and tailing ponds Culmitzsch, Trünzig and Helmsdorf) as well as yellow cake process plants (Crossen, Seelingstädt). Also the overbanks of Zwickauer Mulde River show a clear uranium anomaly. Maps of potassium and thorium concentrations provide information of geological features, but the potassium map apparently also indicates effects of fertilizing.

The measured radiation total counts were converted to radiation dose rates (Figure 2.). The results were compared to Wismut's monitoring data from 1993. The conversion of gamma ray measurements to biological dose rates is based on a mathematical model.

Validating and calibrating airborne data with soil sampling

Compared with airborne measurements, systematic soil sampling and ground surveying are slow and expensive methods. Especially the identification of scattered unknown contaminated spots in large areas by ground surveying is very costly. Airborne gamma-ray measurements are a fast and reliable way of surveying and monitoring radioactive elements. The gamma-ray measurements provide reliable data for uranium, thorium and potassium concentrations in the top decimetres of the earth. One objective of the AERA-project was to assess the accuracy of the airborne gamma-ray measurements. Topsoil samples were collected from sites with interesting airborne anomalies and from suitable background reference sites. The sampling sites comprised flooded banks of the river Zwickauer Mulde, agricultural fields and black coal stockpiles in Oelsnitz.

The overbanks of the Zwickauer Mulde show a clear uranium anomaly, which can be traced throughout the whole test area. The anomaly strength increases near Crossen, a former process plant in Zwickau. The uranium anomaly is stronger in the flood plains than in the riverbed itself because the radioactive particles have been transported during floods and

deposited as overbank sediments. Samples were collected both from the sediments of the active channels and from the riverbanks. The uranium contents of these samples vary between 7 and 66 mg/kg. The readings in airborne uranium data are 10-18 mg/kg). The airborne measurements apparently underestimate high uranium concentrations, because the calibration is normally performed over a homogeneous half space. Anomalies will show up as peaks superimposed on the background reading.

The potassium map shows an anomaly on farmed fields southwest of Zwickau. The equivalent potassium concentrations here are some 50 % higher than those from other agricultural areas. Samples of topsoil were collected in order to validate this anomaly. The samples from the anomalous fields south of Zwickau show potassium concentrations of 25,900 – 43,400 mg/kg while the reference samples contain 13,600 – 23,600 mg/kg. The concentration of phosphorous was 1,130 – 3,710 mg/kg for Zwickau samples and 688 – 1,140 mg/kg for reference samples. This is interpreted as an effect of more intensive use of fertilizers in the fields near Zwickau than in the reference fields. The determined concentrations match very well with the readings of airborne potassium data. The airborne readings of the higher concentrations in Zwickau are 25, 000 - 43, 000 mg/kg.

In Oelsnitz, black coal mining has taken place during centuries, and stockpiles with waste rock are located around the town. One stockpile differs from the others showing high uranium values in the airborne measurements. Soil samples taken from this stockpile produced 76-168 mgU/kg, while other stockpiles showed 3-4 mg/kg. Values from the airborne measurements are, respectively, 17 - 51 mg/kg and 2 - 4 mg/kg. In other words, the low values match very well, while airborne measurements underestimate the high values.

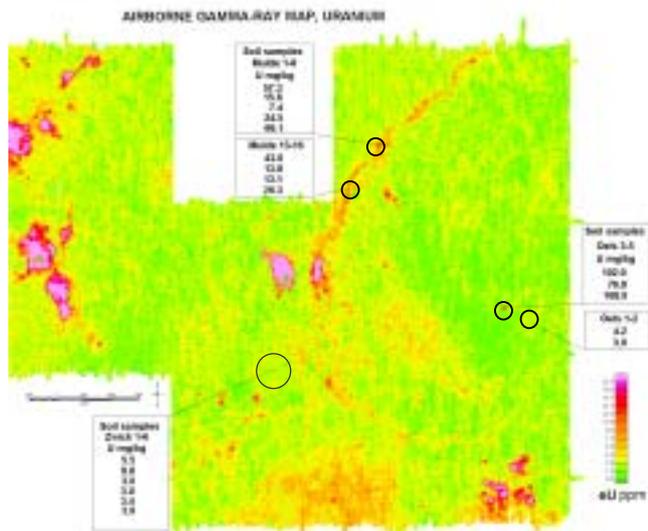


Figure 1. Uranium map from the test site in Germany and results of soil sample analysis. Topsoil samples Mulde 1-16 were collected from the overbanks of Zwickauer Mulde River at sites of uranium anomalies obtained from the air. The overbank samples show significantly higher uranium concentrations than the samples from reference fields (samples Zwick 1-6). Samples Oels 1-5 represent the waste rock produced by black coal mining. Samples 1-2 were collected from a pile without uranium anomaly and samples 3-5 from a pile with a radioactive anomaly. The soil samples show similar contrasts in the uranium concentration as those obtained by the airborne measurements.

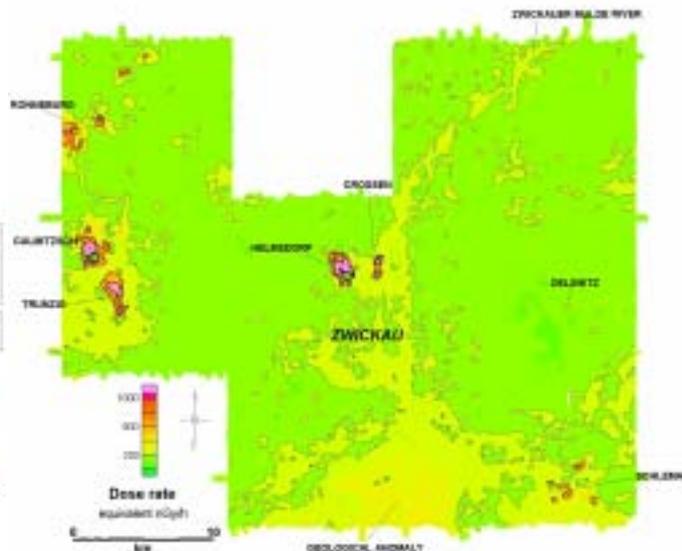


Figure 2. Dose rates (nGy/h) converted from measured total counts. The map shows that 0.4 % of the project area produce doses which may be dangerous for humans. The most contaminated sites are in the vicinities of process plants, tailing ponds and some stockpiles. 1% of the area should not be used for settlement purposes. The radiation level is higher than the background in 36.3 % of the area. Natural geological features caused 20 % of this. The background radiation level covers 62.3 % of the project area.

Hazards for uranium miners and residents

Uranium mining and milling have many environmental impacts. Stockpiles, tailings and other waste deposits may contaminate the environment by release of radium, radon, uranium and other heavy metals, which are in a more mobile form than originally in the bedrock. Chemicals used in enrichment processes and oxidation products such as sulphuric acid may also cause serious contamination.

In early years of uranium mining, the health precautions were poor and workers were exposed to high doses of ionizing radiation due to inhalation of radioactive dusts and radon gas. According to Diehl (2000), the radon concentrations in Wismut's mines were typically 100 000 Bq/m³, with peaks of even 1.5 million Bq/m³. In the 1970's the health protection was improved including a reduction of radiation dose rates to tolerable levels.

Analysis of health data in the East German uranium mining areas showed significantly increased lung cancer incidence rates for men. In cities located very close to mines, increased lung cancer risks were also found for women. For example, in the population of the Thuringian uranium mining district the lung cancer risk is estimated to be 15 per 1000.

Waste rock from uranium mining was in many cases used for road and railroad construction, thereby dispersing radioactive material over large areas. The Saxonian Hartsteinwerke Oelsnitz have, for example, processed 7.58 million tonnes material with uranium concentrations of up to 100 g per tonne. Baukombinat Zwickau used 14.4 million tonnes of wastes from the Crossen uranium mill for road construction. This material had uranium concentrations up to 150 g per tonne and radium contents up to 1.3 Bq/g.

The AERA project could clearly identify some of the areas where tailings containing uranium were used for construction purposes. The most interesting is a former military site where the contamination found by the AERA project has led to postponing the planning of new settlements.

Tailings from uranium mining have also been used for construction purposes in other countries. In the US such tailings were used for foundations of homes, resulting in high indoor radon exposures and increased lung cancer risks. In Eastern Siberia, tailings sands from a uranium mine at Baley (Chita region) were used for the construction of apartment buildings and kindergartens. Radon concentrations in these buildings exceed the 200 Bq/m³ standard up to 37-fold (Diehl, 2000).

Conclusion

Airborne gamma ray measurements provide a good method for quick surveys of small and large areas with natural ionizing radiation or radioactive contaminations. The method is also useful for monitoring remediation works. Radioactive background levels are measured with a high precision. Soil sampling for calibration purposes is required in areas with higher contaminations because the airborne measurement system tends to underestimate high radiation values from small spots.

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Radon in Potable Groundwater: Examples from Norway.

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Abstract

Radon in potable groundwater contributes to radon concentrations in indoor air when degassed and may also have a health impact when ingested. During the 1990s, several surveys of radon concentrations in Norwegian groundwater have been carried out, including a nationwide study by the Norwegian Radiation Protection Authority and the Geological Survey of Norway. 222 of 1601 (13.9 %) investigated boreholes in Precambrian and Palaeozoic crystalline bedrock yielded water with radon concentrations in excess of the recommended action level of 500 Bq/l. The highest levels are usually found in granites (up to 20 000 Bq/l), but concentrations vary considerably between boreholes within each lithology. Groundwater in superficial Quaternary sediments typically has radon concentrations well below the recommended action level. Several effective methods exist for removal of radon from water.

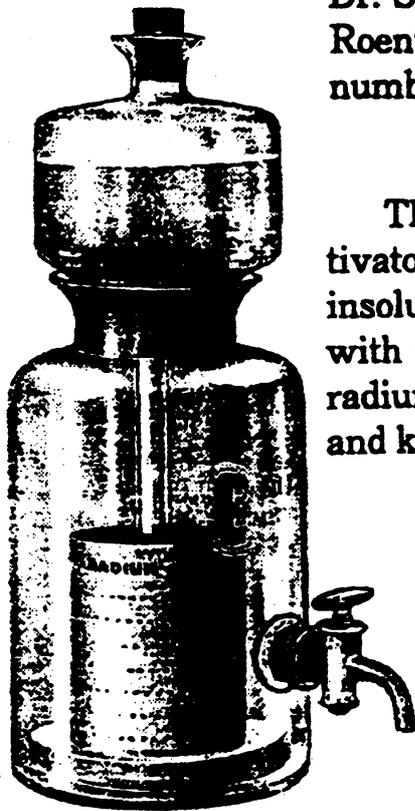
Introduction: Radon in Groundwater

Radon is a naturally occurring radioactive gas. As a member of Group VIII of the periodic table, it is essentially chemically inert. It occurs as three natural isotopes (see Table 1), derived from three different radioactive decay chains, commencing with ²³⁸U, ²³²Th and ²³⁵U. Of the three radon isotopes, ²²²Rn is that most commonly discussed in the context of health risks (and is referred to hereafter simply as "radon"). This isotope has a half-life of 3.8 days, and can thus persist long enough in water and household air to pose a health risk. ²²⁰Rn (thoron) has a much shorter half-life and is commonly regarded as less problematic. However, in some situations (e.g. enclosed spaces in permeable thorium-rich rocks, especially e.g. buildings with indoor wells), thoron can conceivably also be a health issue.

RADIUM THERAPY

The only scientific apparatus for the preparation of radio-active water in the hospital or in the patient's own home.

This apparatus gives a high and measured dosage of radio-active drinking water for the treatment of gout, rheumatism, arthritis, neuralgia, sciatica, tabes dorsalis, catarrh of the antrum and frontal sinus, arterio-sclerosis, diabetes and glycosuria, and nephritis, as described in Dr. Saubermann's lecture before the Roentgen Society, printed in this number of the "Archives."



DESCRIPTION.

The perforated earthenware "activator" in the glass jar contains an insoluble preparation impregnated with radium. It continuously emits radium emanation at a fixed rate, and keeps the water in the jar always charged to a fixed and measurable strength, from 5,000 to 10,000 Maché units per litre per diem.

SUPPLIED BY

RADIUM LIMITED,

93, MORTIMER STREET, LONDON, W.

Telephone: 694 MAYFAIR.

Facing end matter

v

Fig. 1. Apparatus for the preparation of curative drinking water for homes and hospitals. Advertisement from the 1920s.

Table 1. Half-lives of the three natural isotopes of Radon.

Isotope	Common name	Half-life	Decay chain commencing with
^{222}Rn	Radon	3.8 days	^{238}U
^{220}Rn	Thoron	54.5 seconds	^{232}Th
^{219}Rn	Actinon	3.92 seconds	^{235}U

Radon is important in the context of potable groundwater, because the elements thorium and uranium are abundant in some groundwater-bearing rocks, such as granites (e.g. arithmetic mean values of 50.2 ppm and 9.9 ppm respectively in the Norwegian Iddefjord granite (Killeen and Heier, 1975)), and also because radon has a high solubility in water. As with most gases, solubility decreases with increasing temperature (51 vol. % at 0°C and 13 vol. % at 60°C).

Although, today, exposure to radon is associated with health risks (e.g. lung cancer), the element was not always perceived thus. Radon was, not so long ago, considered a desirable, "invigorating" component of mineral waters and spas. For example, the spa at Badgastein in Austria was (and still is) famed for its natural radon-containing mineral waters (at concentrations of up to 3990 Bq/l). At Bath Spa, in England, a funnel-shaped "inhalitorium" was constructed above the mineral water springs so that patients (as recently as the mid-20th Century) could breath in the degassed radon from the water. It was even possible to purchase domestic radonating kits, whereby a radium mineral would release a supplementary dose of radon to domestic drinking water (Albu et al. 1997, see Fig. 1).

Sources of Radon in Groundwater

It might be supposed that radon in groundwater could be derived from two different sources:

- (i) radioactive decay of dissolved radium (the immediate precursor to radon in the decay chain).
- (ii) direct release of radon from the mineral matrix from minerals containing members of the uranium/thorium decay series.

In fact, in most waters, concentrations of radon are far in excess of those that one would expect from mere equilibrium decay of dissolved radium (a rather insoluble element). It is thus believed that radon in groundwater is dominantly derived from mineral sources in aquifer grains or wall rock of fractures. Concentrations of radon in groundwater thus largely depend on six factors (Nelson et al. 1983, Michel 1990, Ball et al. 1991, Albu et al. 1997):

- (i) hydrodynamic factors (e.g. whether groundwater is flowing slowly enough to approach an equilibrium between mineral and dissolved phases)

- (ii) geometric factors. Equilibrium radon concentrations are believed to be inversely proportional to the aperture of a groundwater-bearing fracture.
- (iii) the uranium (or strictly speaking, the radium) content of the aquifer host rock (or fracture mineralisation)
- (iv) the mineralogy of the phases containing the radium and uranium
- (v) possibilities for degassing of radon prior to point of abstraction.
- (vi) concentrations of dissolved radium in groundwater

Figure 2 shows the correlation between dissolved radon and dissolved uranium in Norwegian bedrock groundwater. The correlation is not due to dissolved uranium decaying to release radon gas. Rather, both parameters are ultimately derived from the same uranium-bearing minerals in the aquifer matrix. In other words, uranium-rich granites will often contain groundwater with both high levels of dissolved uranium and dissolved radon.

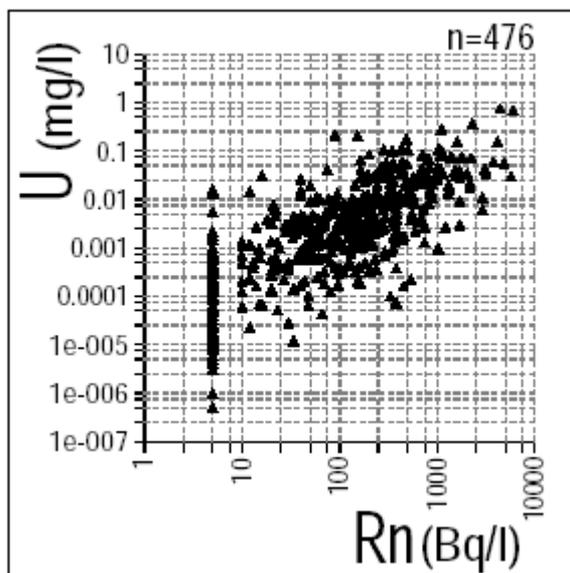


Fig. 2. X-Y plot of radon versus uranium concentrations in Norwegian bedrock groundwater (From Frengstad et al., 2000). Note the log scales.

Exposure Mechanisms

The most obvious pathway for exposure to radon in groundwater is by ingestion (drinking). Some studies have indicated a possible link between radon in water and gastric cancer (Mose et al. 1990), although this has yet to be conclusively proven. Swedjemark (1993) has estimated doses derived from radon in drinking water and believes that the dose from the ingestion pathway is most significant in young children (Table 2).

Table 2. The effective radiation dose from radon in household water. The proportion of the dose derived from aerated (and inhaled) radon is compared with the proportion derived from digestion of the water for infants, children and adults. Total dose should not exceed 1 mSv pr. year on a life-time average. Source: Swedjemark (1993).

Radon in water [Bq/l]	Target Group	Inhalation dose [mSv/year]	Ingestion dose [mSv/year]	Sum dose [mSv/year]
100	Infants 1 year	0,4	0,7	1,1
	Children 10 years	0,4	0,15	0,55
	Adults	0,4	0,05	0,45
1000	Infants 1 year	4	7	11
	Children 10 years	4	1,5	5,5
	Adults	4	0,5	4,5

When radon-rich groundwater enters a home, there is also potential for degassing of radon from water to household air, especially as the water heats up and the radon becomes less soluble. In particular, radon is degassed extremely effectively in household appliances such as dish-washing machines and shower units. Figure 3 indicates that, on turning on a shower (which utilises radon-rich groundwater), concentrations of radon in the air increase very rapidly. After the shower has been turned off, radon concentrations in air fall only slowly and persist above recommended maximum levels for a long time.

The Norwegian Radiation Protection Authority has recommended an action level of 500 Bq/l for radon in domestic water, and 200 Bq/m³ in household air (NRPA, 1995).

Radon concentration in bathroom air (Bq/m³)

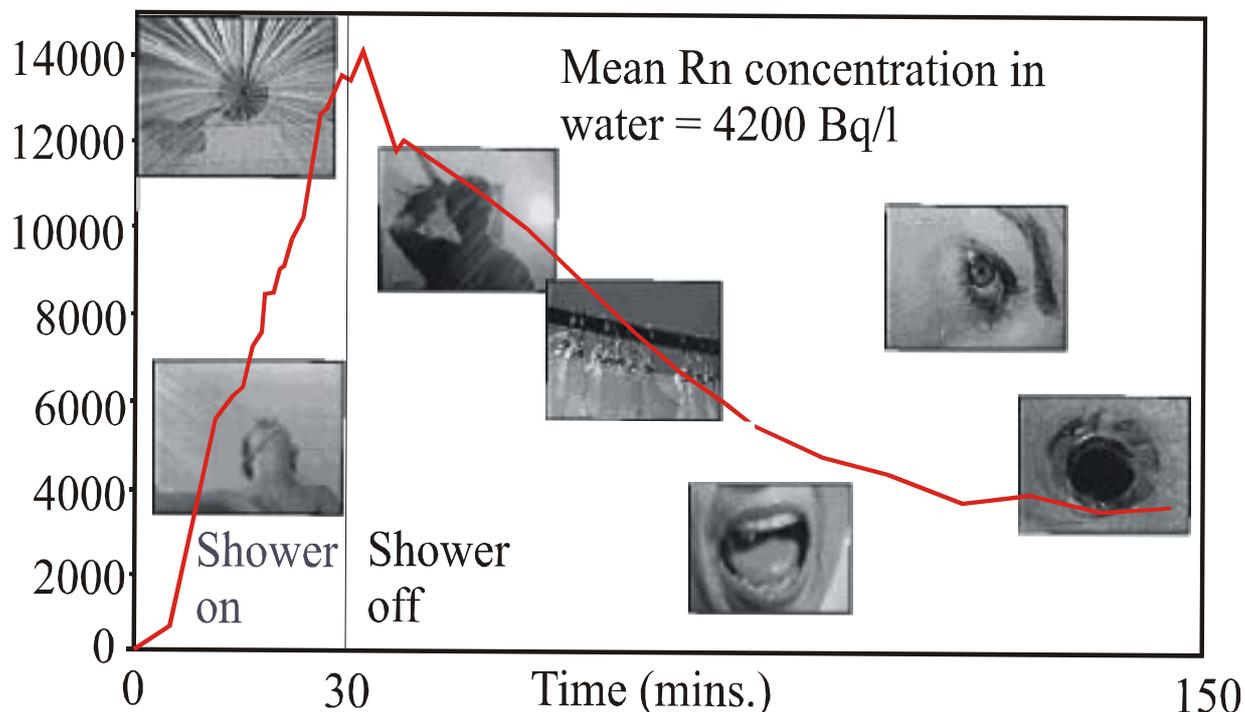


Fig. 3. Effect of Rn-containing shower water (4200 Bq Rn/l) on the concentration of Rn in the bathroom air. (After Strand and Lind, 1992).

Surveys in Norway

Probably the earliest investigations of radon in Norwegian groundwater were carried out by Staw et al. (1989) and Strand & Lind (1992). This was followed by the Geological Survey's pilot project in 1992-93 where around 30 water samples were collected from wells in south-eastern Norway and Trøndelag (Banks et al. 1995a,b). In this study the Iddefjord Granite aquifer was demonstrated to contain a number of boreholes yielding water with disturbingly high radon concentrations. A larger (150 samples) project continued this work in the counties of Hordaland and Vestfold, again demonstrating that radon can be a problem-parameter in Norwegian crystalline bedrock groundwater (Reimann et al. 1996, Morland et al. 1997). Sampling of wells in Quaternary superficial deposits (sands, gravels, tills - see below) was published by Morland et al. (1998). During the period 1996-1999, the Norwegian Geological Survey supported the national groundwater quality mapping project, SPAGBIFF (*Systematisk Prøvetaking Av GrunnvannsBrønner i Fast Fjell*), where radon was one of the parameters analysed (by the Norwegian Radiation Protection Agency, NRPA). During this project, some 1600 quality-controlled samples of water from boreholes/wells/springs in crystalline bedrock

were analysed, together with 72 samples of groundwater from Quaternary superficial deposits. Results of SPAGBIFF are published by Banks et al. (1998a,b, 2000) and Frengstad et al. (2000, 2001). NRPA continued to receive groundwater samples and a total of about 3500 samples have been analysed for radon (Strand et al., 1998).

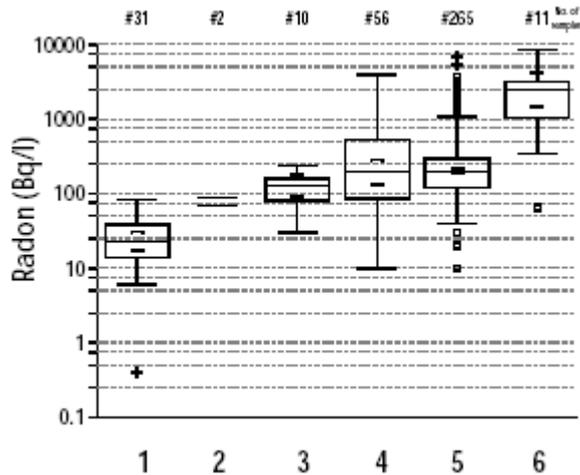


Fig. 4. Boxplots for concentrations of radon in water. (1) Ground water from Quaternary deposits. (waterworks supplying >1000 persons), (2) groundwater from crystalline bedrock (waterworks supplying >1000 persons). (3-6) Groundwater from boreholes in crystalline bedrock in the counties of (3) Trøndelag, (4) Hordaland, (5) Vestfold, and (6) Østfold (Iddefjord granite). Data from Reimann et al. (1996), Morland et al. (1997, 1998), Banks et al. (2000). For an explanation of the Boxplot, see Appendix A.

Radon in Groundwater in Superficial Deposits

Studies by Morland et al. (1998) and Banks et al. (1998b) have involved sampling and analysis of groundwaters from wells and boreholes in Quaternary superficial deposits (loose sands, gravels, tills etc.) in Norway. These aquifers are important because they support high-yielding wells and form the basis for many of Norway's largest public groundwater works.

Although the authors of these studies were able to identify a tentative correlation between radon concentrations in groundwater and the composition of the underlying crystalline bedrock, the concentrations were typically significantly below the recommended action level of 500 Bq/l (Fig. 4).

It is thus, in a Norwegian context, groundwater from crystalline bedrock that poses a potential radon health risk, rather than groundwater from superficial deposits. The reason for this is probably that intensive chemical and mechanical weathering have removed most of the uranium-containing minerals from Quaternary sands and gravels (which are overwhelmingly dominated by quartz clasts), while in the glacially scoured, fresh bedrock, uranium mineralisation persists.

Radon in Groundwater in Crystalline Bedrock - Lithological Dependence

During the aforementioned SPAGBIFF study (Banks et al. 1998a), the distribution of radon concentrations in 1601 sampled crystalline bedrock groundwaters could be plotted on cumulative frequency diagrams. The diagrams indicate a highly skewed (some would say, quasi-log-normal) distribution, the bulk of the samples having modest radon concentrations but with a not insignificant number of extremely high outliers (up to 20,000 Bq/l). Some 13.9 % of the samples exceeded the recommended action level of 500 Bq/l (Figure 5).

When the data set was split into different lithological units, clear differences began to emerge. While, for each individual lithology, one could still find a wide range of values, exhibiting a heavily skewed pattern on the cumulative distribution curve, the position of the curve differed between differing lithologies. For example, the anorthosites of the Egersund area exhibited a median radon concentration of < 10 Bq/l, whilst the Iddefjord granite of south-eastern Norway had a median of some 700 Bq/l.

Because of the range of values present in each lithology (depending, presumably, largely on local hydrodynamic and mineralogical factors), it is *not* possible to predict that a specific well drilled in a particular formation will not have a problem with radon, nor is it possible to state that all wells in, for example, the Iddefjord granite will have a problem. It is, however, possible to predict the probability of a given lithology giving rise to a potential problem. For example, in the Iddefjord Granite, we can say (on the basis of SPAGBIFF data) that there is a 70 % chance that a well will yield water exceeding the recommended action level of 500 Bq/l radon.

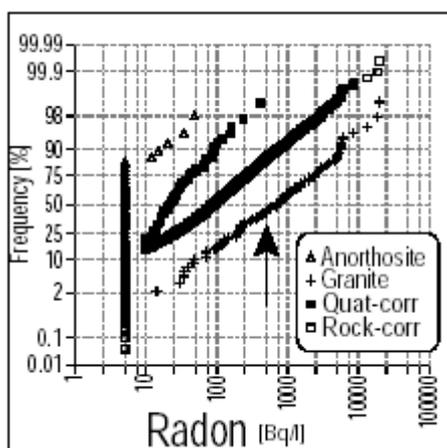


Fig. 5. Cumulative frequency distribution diagram for radon.

□) the Rock-corr (n=1601) data set of groundwater from crystalline bedrock boreholes,

■) the Quat-corr (n=72) data set of Quaternary sedimentary groundwater,

+ Precambrian granites (n=76, subset of Rock-corr) and

Δ) Precambrian anorthosites (n=34, subset of Rock-corr).

The arrow on the diagram show the Norwegian recommended action level for Rn in potable water (500 Bq/l).

Time-Dependence of Radon Concentrations

In 1999, five boreholes in crystalline bedrock in the Bergen area of Norway were sampled every two weeks, throughout a period of one year, to determine the time-variability of radon concentrations in groundwater (Nilssen, 2001). The five selected boreholes spanned a range of radon concentrations from modest (<100 Bq/l) to high (c. 5000 Bq/l). Results are shown in Figure 6. It will be noted that radon concentrations in four of the boreholes were surprisingly stable. In borehole 5, they were subject to major fluctuations correlating with rainfall events. Close inspection of the borehole revealed that, during strong rain, surface run-off water was running directly into the borehole, diluting the radon-containing groundwater.

It is naturally difficult to draw general conclusions from this study, but one might expect unstable radon concentrations in boreholes whose water has a low residence time compared with the half-life of radon.

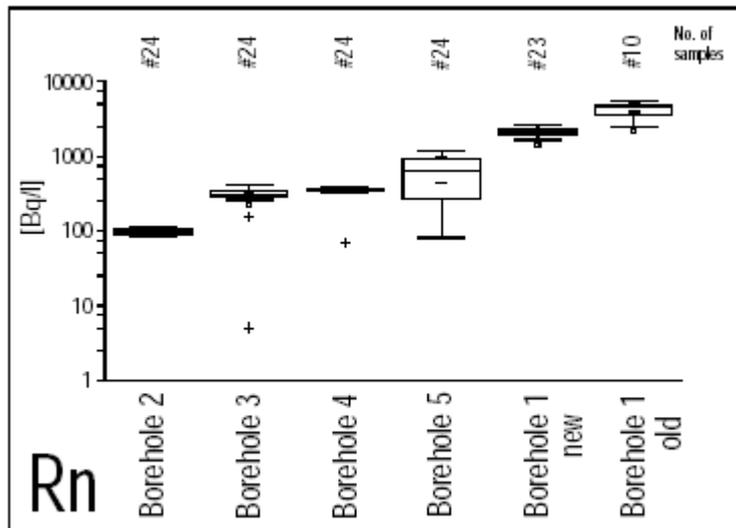


Fig. 6. Boxplots showing the seasonal variation of radon concentrations in waters from five boreholes in the Bergen area. Sampling was done every 2 weeks during one year. At location 1 the borehole was replaced with a new one during the sampling period. For an explanation of the Boxplot, see Appendix A.

Removal of Radon in Potable Groundwater

There exist a number of methods for treating radon-containing water, of which several are reported to have a removal efficiency of over 95%. The methods are essentially based on one (or a combination of) the following:

- (i) aeration: to remove radon from water to the gas phase prior to entry to the household
- (ii) storage: a storage period which is significant in comparison to radon's short half-life (3.8 days) ensures decay of radon to short-lived isotopes (lead, polonium etc.) which are neither degassed to air nor readily adsorbed during human ingestion.
- (iii) filtration: activated carbon filtration and reverse osmosis have been shown to be effective at removing radon. These methods are expensive, especially for large quantities of water, and require a certain amount of maintenance.

Of these methods, aeration is possibly most suited to treatment of radon from wells in crystalline bedrock. Aeration units are typically based on bubbling or cascading water through a high-surface area aeration medium. Units are available which are reported to have a 99% radon removal efficiency (although this depends on radon concentration and water flow). After aeration, water should be stored for at least 1 hour, before use, in order to allow daughter products (with short half-lives) to decay. Further information on treatment of radon in water is found in Banks et al. (2000).

Conclusions

Radon in drinking water may give doses of concern by ingestion, especially in young children. Through showers and washing machines, radon in household water is also released to the indoor air, which may subsequently be inhaled.

Radon is ubiquitous in Norwegian crystalline bedrock groundwaters. The radon concentrations vary significantly between boreholes in the same lithology, possibly largely due to hydrodynamic factors. The highest levels of radon in groundwater are found in uranium-rich granites, but high levels are found in most other lithologies as well. Precambrian anorthosites is the only investigated lithological group where the probability of finding radon concentrations above the recommended action level is almost nil. We thus recommend that every household, whose potable water is derived from bedrock aquifers, requisition a water analysis.

Surveys of groundwater from Quaternary sand and gravel deposits reveal that radon is not a major problem in these aquifers. It is such aquifers which support the majority of larger public groundwater supply works in Norway.

An investigation of 5 boreholes in the Bergen area suggests that radon concentrations in bedrock groundwater are rather stable through the year. However, in cases where water residence times are low, some degree of fluctuation might be expected.

There exist several methods for removing radon from water, of which a combination of aeration and subsequent short storage seems to be the most efficient.

Appendix A

The boxplot provides a graphical data summary where median, quartiles, spread, and data outliers are displayed. The box contains the mid 50 % of all data where the median value is marked with a line that divides the box. The brackets above and below this line denote a robust 95 % confidence interval on the median. The upper and lower ends of the box (called "hinges") represent the 75 % quartile and the 25 % quartile, respectively. Lines (called "whiskers") are drawn from the ends of the box towards the maximum and minimum values, respectively, each containing about 25 % of all data. The whiskers extend up to 1.5 times the length of the box and outlying data points are plotted as crosses (near outliers) and squares (far outliers). Boxplot is a useful presentation technique for comparison of different datasets and for revealing skewness of the distribution and outlying data points.

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High Indoor Radon Concentrations at some Swedish Waterworks

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Abstract

High indoor radon concentrations are rather common in buildings used for water treatment. When raw water is processed in an open system, radon escapes from the water to the indoor air of the buildings. The staff of the waterworks often have their offices in the building where the water is processed. If large volumes of water are processed, evaporated radon may reach the workplaces. Indoor radon concentration may in this way be very high, even if the radon concentration of the raw water is moderate. Groundwaters from aquifers in bedrock and soil as well as surface water that have been infiltrated through deposits of sand or gravel, may cause high indoor radon levels. However, in surface water taken directly from lakes or rivers the radon concentrations are too low to cause problems. Three waterworks in central Sweden have been studied, Ludvika, Fredriksberg and Kolbäck. The radon concentrations in the raw water of these waterworks range from 85 Bq/l to 300 Bq/l. Average indoor radon concentrations exceeding 17,000 Bq/m³ have been found in the waterworks at Ludvika with peaks of almost 37,000 Bq/m³. In Kolbäck, radon concentrations up to 56,000 Bq/m³ have been detected. It is quite possible that employees at waterworks can receive doses exceeding 20 mSv per year (calculated according to the ICRP dose conversion convention). The paper reports data for radon and gamma radiation at the waterworks and discusses methods for reducing the indoor radon concentrations.

Introduction

At waterworks, large volumes of water are usually treated. The water is normally aired, often in open systems, and chloride and other chemicals are added. Radon dissolved in the water is inevitably released to the indoor air of the waterworks.

In Sweden, about 50 per cent of the drinking water is surface water, 25 per cent is groundwater and 25 per cent ground or surface water infiltrated into natural sand and gravel deposits, e.g. eskers. The country has approximately 2,100 public waterworks. Relatively few large waterworks, predominantly using surface water, serve the majority of the population in densely populated areas. Most waterworks in Sweden, however, are relatively small. A large

number of these use groundwater or infiltrated water. 70 per cent of these serve less than 1,000 consumers each (1).

The radon levels in surface waters are usually very low (less than 1 Bq/l). Normal radon concentrations in groundwater in soil aquifers in Sweden range from 10 to 300 Bq/l. In drilled wells typical radon levels are 50–500 Bq/l, in uranium-rich granites, however, 300–4,000 Bq/l. The maximum radon concentration found in water from a drilled well in Sweden is 89,000 Bq/l (2).

In 1999 the local health officer of the Ludvika municipality in central Sweden informed the Swedish Radiation Protection Authority (SSI) that indoor radon levels at the waterworks in Ludvika and Fredriksberg were very high. In 2000, representatives from SSI visited these waterworks as well as the waterworks in Kolbäck to follow up this information.

The personnel at the waterworks normally work a couple of hours per day with surveillance of pumps and filters, cleaning reservoirs and handling chemicals used in the water treatment processes. The same personnel very often serve several waterworks in the same area. It is common for other municipal workplaces, such as offices, to be included in the waterworks buildings.

Normal concentrations of ^{226}Ra in groundwater in Sweden vary between 0.001 Bq/l and 0.3 Bq/l. In uranium-rich granites the levels are higher, a maximum of 8 Bq/l has been found in a drilled well (2). The dissolved radium is often precipitated together with iron- and manganese- hydroxide and may be deposited inside tubes and pumps. Radon progeny will also be deposited in filters containing activated charcoal and sand. Elevated gamma radiation from filters and pumps may therefore be a problem. Sometimes filters contain so much radium that they will act as secondary radon sources for low radon waters entering the filter.

Inspections and measurements

The Ludvika waterworks

This waterworks serves the small town of Ludvika. It is situated on an esker (a postglacial formation of gravel and coarse sand, highly permeable to both air and water). The raw water originates in a small lake from which it is naturally infiltrated into the esker, Fig. 1. From the esker it is pumped up using cased wells, sprayed into small ponds in the vicinity of the waterworks and thereafter re-infiltrated into the esker, Fig. 2. The purified water is pumped into a mixing basin situated under the waterworks building where chemicals are added. Air from the basin can reach the premises through an inspection opening in the bottom floor, Fig. 3. From the mixing basin, the water is pumped into a 3,000 m³ reservoir situated below the waterworks building. The treated water is pumped into a high reservoir in the town before

reaching the consumers. The waterworks has a staff of five full or part time employees working between 200 and 800 hours per year.

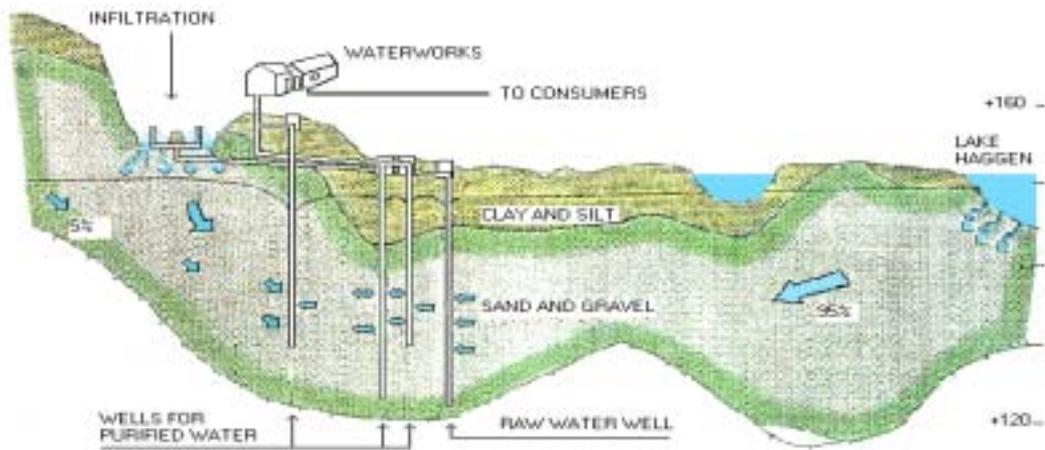


Fig. 1. The Ludvika waterworks



Fig. 2. Re-infiltration basin at the Ludvika waterworks



Fig. 3. Inspection opening to the mixing chamber

On average, 6,000 m³ of water passes the waterworks per day. The radon concentration is found to be 85 Bq/l in the raw water and 75 Bq/l in the treated water. According to the measurements performed by the municipal health authorities the average indoor radon levels in different rooms in the waterworks building varied from 1,200 Bq/m³ to 18,000 Bq/m³. Maximum values exceeding 35,000 Bq/m³ have been recorded, see Table 1.

Table 1. Radon gas concentrations (Bq/m³) in different parts of the waterworks building in Ludvika according to measurements performed by the municipal authorities

Location	Before remedial measures Average	Before remedial measures Maximum	After remedial measures
Control room	4,250	10,860	
Above mixing basin	17,870	36,900	40
Cellar outside reservoir	8,150		100
Canteen	1,200		40

The water is transported in a closed system until it reaches the mixing basin and the reservoir. The water flow in the mixing basin is turbulent and radon is released from the open water surface to the air in the room situated above the mixing basin from where it spreads to

other parts of the waterworks building. The reservoir is covered with a concrete roof. In the reservoir, radon is released from the water surface to the air contained between the water surface and the roof. When the water surface in the reservoir is raised as water is pumped in, the radon-rich air is forced via the mixing basin up into the building. This is the reason why the radon concentrations in the building vary so much, see Fig. 4.

To reduce the indoor radon levels, a supply/exhaust ventilation system has been installed with a local extraction point (430 litres of air per second) just above the water surface in the mixing basin, see Fig. 3. As can be seen from Table 1 and Fig. 4, the remedial measures have been quite successful. The indoor radon levels are now 40–100 Bq/m³.

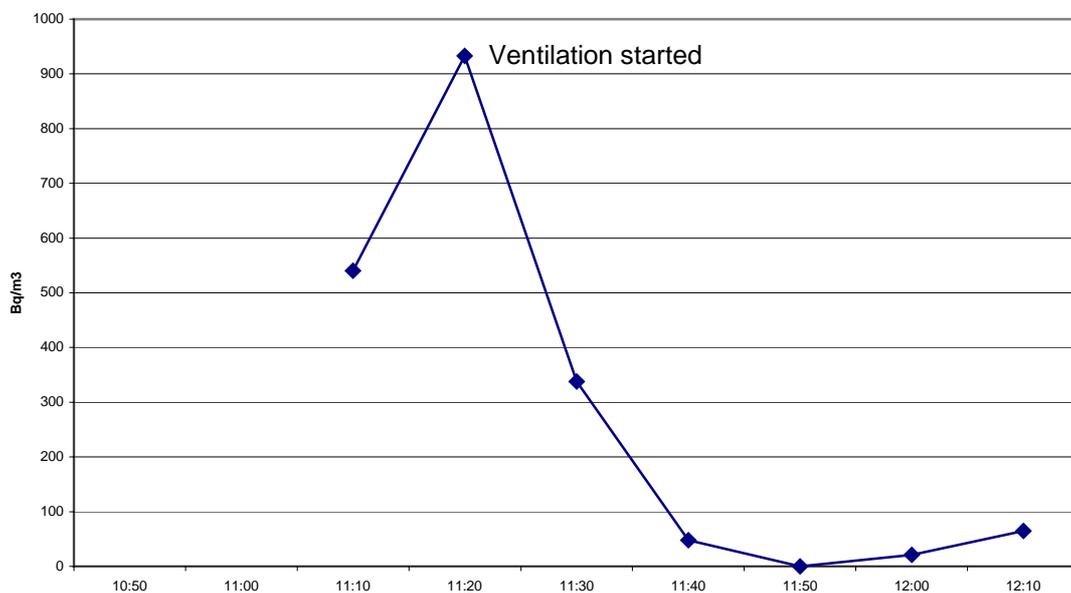


Fig. 4. An example of time variations in the radon content in air close to the mixing chamber at the Ludvika waterworks

The Fredriksberg waterworks

The waterworks supplies the village of Fredriksberg and the neighbouring area with drinking water. It is situated on the shore of a small lake. The raw water rises into cased wells from an esker on a small island in the lake and it is pumped into the waterworks. The raw water is not aired or further filtered before it reaches the waterworks. In the plant, potassium permanganate and soda are added, after which the water is aired and flocculation takes place in open basins. The flocculent precipitate is removed by an open contact filter. As a result, open water surfaces are exposed in the main hall of the waterworks with consequent release of radon into the indoor air. The water is then treated in closed sand filters and stored in a reservoir situated below the waterworks building, until it is pumped into the distribution system. Apart from the main water treatment hall, the building also contains a small

laboratory and an office. The door between the main hall and other parts of the building is normally closed.

Two people work regularly at the waterworks, normally spending about five hours per day, corresponding to about 1,000 hours per year.

600–700 m³ of water are treated per day. The radon concentration of the raw water was earlier found to be 110 Bq/l. Samples taken after the sand filters and from the outgoing water contained 40 Bq/l and 15 Bq/l, respectively, while arbitrary samples from the distribution network contained 35 Bq/l.

Before any remedial measures, the average radon concentration in the air of the main waterworks hall was 11,200 Bq/m³ and 7,000 Bq/m³ in the laboratory. With the new ventilation system, having the extraction point just above the water surface of the open contact filter, the radon levels in the main hall and the laboratory were reduced to below 400 Bq/m³. In very cold weather, however, the temperature in the building becomes too low and the ventilation system has to be temporarily shut off, leading to increased radon levels.

During the visit of SSI personnel, we made measurements in the main hall and the laboratory using continuous radon gas monitors, see Fig. 5. The doors to the plant had been closed for several days prior to our visit and the ventilation system had been shut off.

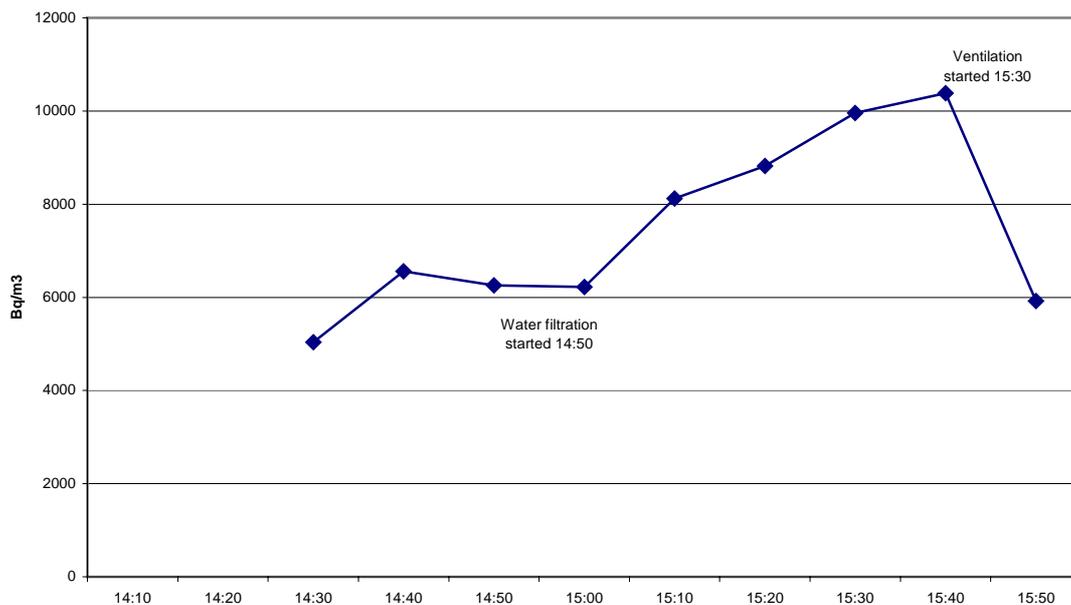


Fig. 5. Time variations in the contents of radon in air in the main hall at the Fredriksberg waterworks

Gamma radiation measurements were performed around the water treatment equipment. Elevated gamma radiation levels were found close to some of the pumps, (0.2–0.4 μSv/h), and close to a cooling radiator of a dehumidifier (0.8 μSv/h). The gamma radiation was caused by radon progeny deposited on the cooling fins of the pumps and in the radiator.



Fig. 6. The Kolbäck waterworks



Fig. 7. Equipment for intense aeration of the water at the Kolbäck waterworks

The Kolbäck waterworks

This waterworks supplies drinking water to the village of Kolbäck and the surrounding area. The waterworks is situated at the edge of a very long esker, Strömsholmsåsen, running through Kolbäck. The raw water is brought up in cased wells directly from the esker into the waterworks for treatment and subsequent distribution to the customers. The treatment plant was finished in 2000, see Fig. 6. Before that, the water was distributed from an old waterworks situated close to the new one. In the old plant the water was pumped through a closed system directly into the pipeline network without airing or any other treatment. The radon concentration of the water was then 200–300 Bq/l. Since Sweden has an action level of 100 Bq/l for radon in public drinking water, the municipal authority had to take remedial action to reduce the radon level in the distributed water and a new plant was built.

Equipment for intense aeration of the raw water, supplying 5,500 m³ air per hour, was installed in the new waterworks building, Fig. 7. After airing, the water is stored in a 150 m³ reservoir situated under the building. In direct connection to the main hall of the waterworks there are a small control room and an office. Normally, the door between the water treatment hall and the rest of the building is closed.

The average throughput is about 1,500 m³ water per day. The radon concentration of the raw water is 200–300 Bq/l. After passing the airing equipment, the radon concentration was found to be 90 Bq/l. The radon concentration of the distributed water is about 50 Bq/l.

When the new plant was put in operation, the radon concentration in the air in the main hall was monitored. Since the concentration was found to be high, some preliminary action was taken, including installing an additional fan to increase the ventilation rate and some sealing work to prevent the passage of radon from the reservoir. Measurements performed by the municipal authorities showed radon concentrations exceeding 40,000 Bq/m³ in the main hall prior to the installation of the additional fan. Fig. 8 shows the effect of the preliminary measures by which the concentration was reduced from 40,000 to less than 10,000 Bq/m³ during the period 27 April to 3 May 2000. In connection with our visit to the plant the ventilation was shut off in order to monitor the highest values. During the period 5–9 May 2000, the mean concentration was around 30,000 Bq/m³. The short time variations reflect the effect of pumping the water in and out from the reservoir below the building. During our visit, supplementary measurements were taken confirming the values obtained by the municipality and advice was given on how further to reduce the radon level.

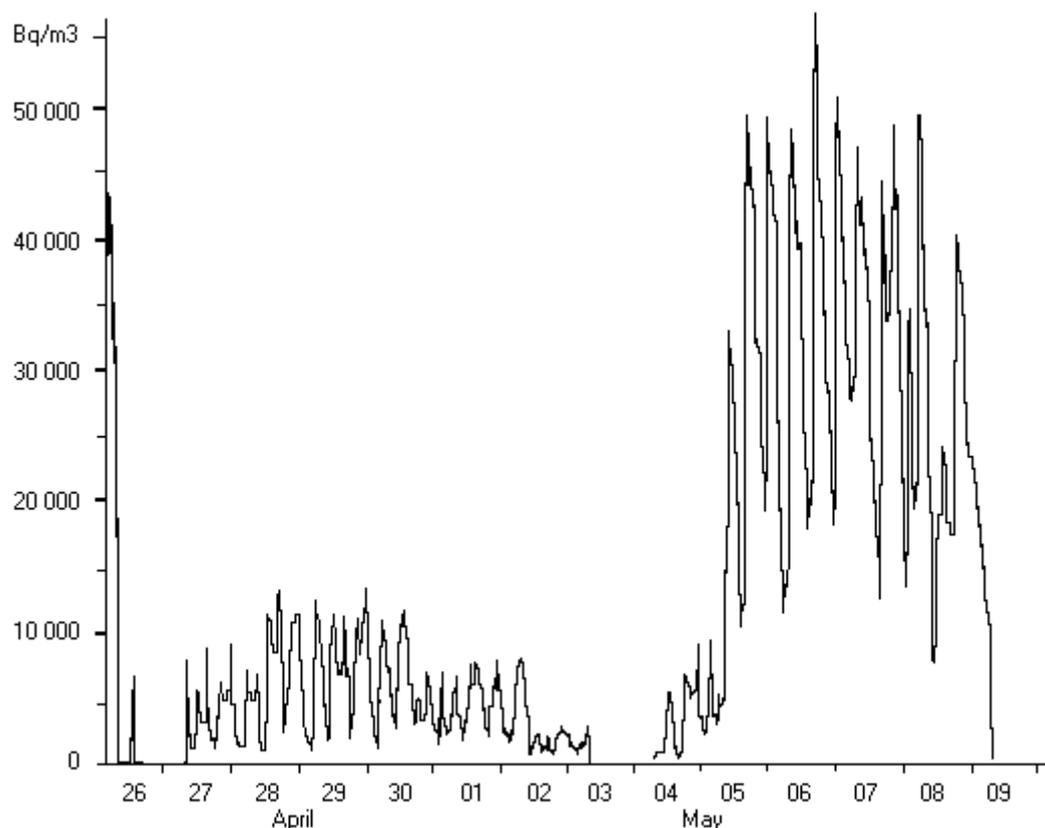


Fig. 8. Results of radon gas measurements in the main hall at the Kolbäck waterworks

Gamma radiation measurements were performed near the water treatment equipment and filters but no elevated levels were found.

Five employees work at the plant. Normally one person performs maintenance and supervision about half an hour per day, five days a week. The total working time per year is estimated to be about 1,000 hours.

Conclusion

The study shows that in waterworks there is a substantial risk for high indoor radon concentrations when large volumes of groundwater or artificially infiltrated surface water are treated indoors in open systems. The radon concentration in the raw water does not necessarily have to be high for the indoor radon levels to exceed 400 Bq/m^3 , which is the action level for radon at workplaces in Sweden. Radon can be forced into the premises by changes in the water level in an enclosed reservoir. This can also give rise to substantial diurnal variations in the indoor radon concentration. The examples show that it is important to control the release of radon from open water surfaces to the indoor air. In the Ludvika waterworks the problem was successfully solved by introducing a ventilation system with a suction point immediately above the open water surface at a small shaft connecting the

reservoir with the building. In the Fredriksberg waterworks the open surfaces of the filters are a problem. In the Kolbäck waterworks the indoor air radon levels were very high, even though the aerating device was entirely contained. Most of the radon that entered the building was released from the already treated water in the reservoir in the same way as in Ludvika.

It is obvious that even well designed water treatment systems may have high radon levels in the waterworks buildings. We recommend that indoor radon levels be measured in all premises where large volumes of groundwater or artificially infiltrated surface water are treated. Measurements should also be made in neighbouring premises. Installed mitigation systems should be checked regularly and the measurements should be repeated every second year or so. There is a risk for high indoor radon concentrations at all workplaces where large volumes of groundwater are used or treated indoors. Possible examples of other workplaces where similar problems could occur are breweries, indoor swimming-pools, food processing industries and laundries.

An estimation of the dose (according to the ICRP dose conversion convention), shows that it is quite possible that employees at waterworks could receive doses exceeding 20 mSv per year.

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This work has also been presented at the Third International Symposium on Naturally Occurring Radioactive Materials, NORM III, Brussels, 17 – 21 September, 2001.

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Radon Concentrations in Norwegian Dwellings

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A nation-wide survey of radon concentrations in Norwegian dwellings was undertaken in the period 1987-89. In this survey, radon measurements were made by CR-39 etched track detectors (six months integration time) in the main bedroom of approximately 7500 randomly selected dwellings built before 1980. The annual average radon concentration in Norwegian bedrooms was calculated to 51 Bq/m³, and 3.7 % of the results exceeded 200 Bq/m³. In a large proportions of single-family houses (including detached, semi-detached, row and terraced houses), the living room and the kitchen are located on the ground floor while the bedrooms are on the first floor. In most cases the radon concentration is higher on the ground floor than on the first floor, and there may also be differences between bedrooms and other rooms on the same floor owing to different ventilation conditions. An additional factor, that could have influenced the measurements, was that the winters 87-89 were considerably warmer than normal. Based on these considerations, the annual average radon concentration in Norwegian dwellings was estimated to be between 55 and 65 Bq/m³, and it was further estimated that close to 5 % of the housing stock exceeded 200 Bq/m³.

In the period between October 2000 and May 2002 measurements of radon were performed in approximately 29,000 dwellings in Norway. In this survey, 114 out of the 435 municipalities of Norway participated. In each municipality measurements were made in between 2% and 10% of the housing stock, depending on the size of the municipality and the population density. However, the dwellings were randomly selected and it is assumed that there is no bias owing to the sampling procedure in the municipalities that participated. The measurements were made by etched track detectors (CR-39), one in each dwelling. The results show that there are significant geographical variations, both between municipalities and within each municipality. The population weighted annual mean radon concentration was calculated to 89 Bq/m³. 9 % and 3 % of the dwellings had higher levels than 200 Bq/m³ and 400 Bq/m³, respectively. By comparing these results municipality by municipality with the results of the nation-wide survey 87-89, it was concluded that the mean radon concentration in the present housing stock is 70-75 % higher than twenty years ago.

A more detailed presentation and discussion of the results will be submitted for publication in an international journal by the end of 2002. A brief discussion of the results have been published in the report series of the Norwegian Radiation Protection Authority (Strand et al 2001).

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Proposal for a New Radon Programme for Sweden

The Swedish Radon 2000 Commission's Report

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Introduction

In 1999 the Swedish Minister of Environment appointed a commission to investigate the radon problem in Sweden and propose cost-effective actions to reduce the radon levels in drinking water and indoor air of dwellings, pre-schools and schools. The proposals of the commission fall into three categories: 1) a prospective environmental-quality standard regarding radon in indoor air, 2) an expanded system of grants for measures against high radon concentrations, and 3) an extensive information campaign and training programme.

Environmental-quality standard for radon in indoor air

In order to protect human health the Commission proposes a Government-defined environmental-quality standard relating to radon in indoor air in dwellings, pre-schools, schools, etc. After a final date specified in the standard (20 years from now for single-family dwellings), the compulsory maximum limit of 400 Bq/m³ for radon-gas concentration will apply. This means that property-owners who – despite the generous grants available – have failed to measure their radon concentrations and reduce excessive levels if necessary, may be punished by a fine. The municipalities already have legal justification in the Swedish Environmental Code for obliging property-owners to implement radon-reducing measures if concentrations exceed the action level of 400 Bq/m³. However, measurements may be made compulsory only where elevated radon concentrations are suspected. The novelty of the environmental-quality standard is that it pressures the municipalities to perform their supervisory function properly.

Grant system for reducing radon contents in indoor air and drinking water

A new system of grants for radon-reducing measures is proposed. For single-family dwellings, the homeowner receives 65% of a reasonable cost of measures during the first ten years. The maximum level of grant for this period is set at SEK 25,000 (2.500 EUR). In the subsequent five-year period, the grant is set at 50% of the costs, up to a maximum of SEK 15,000, and in the last five years at 25%, up to a maximum of SEK 10,000.

The Commission proposes that measures be undertaken in relation to the radon source. The execution of such measures should be supervised by the county administrative boards. The current supervision by the municipalities has not worked particularly well, since many municipalities lack personnel with adequate skills. It will be simpler to maintain the requisite skills at 21 county administrative boards than at 289 municipalities.

A grant system is also proposed for measures to reduce radon in multi-family dwellings. The system is intended to include both residential units with renting rights and flats with tenant-ownership rights. Grants are provided at 50% of reasonable cost. The grants are temporary and scheduled to expire on the final date specified in the environmental-quality standard (a ten-year limit is proposed for multi-family dwellings). A grant system is also proposed for measures against high radon levels in schools, pre-schools, after-school recreation centres, etc. In this case grants will correspond to 25% of reasonable costs. Also these grants are temporary and due to expire on the closing date proposed in the environmental-quality standard (five years). Finally, a temporary (five-year) grant is proposed for measures against high radon contents in drinking water, at a rate of 50% of a reasonable cost, but maximum SEK 5,000.

The Commission proposes setting up a national data register for radon contents in indoor air, at the National Land Survey. This register should be linked to the property-data system. Companies that carry out the measurements would report their results directly to the register. A national register for the contents of radon in soil and water should be run by the Geological Survey of Sweden (SGU). Swedish estate agents will be obliged to inform prospective property buyers of radon levels in houses for sale.

Improved provision of information and extensive training programme

The Swedish Radiation Protection Authority (SSI) and other relevant public agencies are requested to draw up revised information material on radon. A radon portal on the Internet will be created to collect information on radon issues. In co-operation with the other public agencies concerned, SSI will develop a training programme on radon, radon-risk assessments and anti-radon measures for municipal officers.

Implications of the proposal

The aggregate costs of measuring radon in homes, schools and pre-schools are estimated at SEK 800 million, of which measurements in single-family homes account for SEK 500 million. The estimated costs of abatement amount to SEK 2.8 billion, of which measures in single-family homes make up the greater part (SEK 2.3 billion). In addition, there will be increased costs of energy for installations such as fans etc. amounting to around SEK 10 million a year and, in due course, maintenance costs (replacement of fans etc) totalling roughly the same amount annually. The municipalities are expected to incur roughly a 30% increase in

the workload for their health protection, the cost of which is estimated at about SEK 10 million a year.

Public finances will rise to roughly SEK 110 million a year to be spent on radon grants during the first ten years. State expenditure will then fall sharply to around SEK 30 million annually in years 10–15 and SEK 7 million in the last five-year period.

Property-owners will have to cover costs of radon measurements and, where radon concentrations exceed 400 Bq/m³, of radon mitigation. At present, it costs SEK 200–500 to measure the radon concentration in a home. The cost of mitigation varies, depending on the radon source and design of the building. Remediation of a single-family dwelling with soil-radon problems normally costs SEK 10,000–25,000. If building materials are the main source of radon, installation of a mechanical ventilation system is required in most cases. This usually costs SEK 20,000–60,000 per house. Reducing radon concentrations in flats in multi-family dwellings normally costs SEK 5,000–20,000 per flat.

Reservations from three property-owner representatives

Experts from the Swedish Association of Private House-Owners (SAPHO), the Swedish Federation for Rental Property Owners (SFRP) and the National Federation of Tenants' Savings and Building Societies (HSB) have expressed reservations against parts of the Commission's proposals. The spokesman from the SAPHO is critical to those portions that involve applying coercive measures against individual property-owners, such as compulsory measurement of radon at the property-owner's expense. He concludes: 'It is no reasonable proportion between the objectives to be attained and the means one has to adopt. Measures against radon should, therefore, be restricted to the provision of information and grants that can induce property-owners to take remedial action against radon on a voluntary basis.'

HSB's representative calls for a comprehensive approach in assessing domestic risk. He questions whether it is reasonable to measure radon in all residential buildings, and he too concludes that there is no reasonable proportion between the objectives that may conceivably be attained and the means that public authorities are prepared to adopt.

The representative of the SFRP states that the best way of utilising society's resources in health problems is to concentrate on vigorous measures to combat smoking, which would also reduce the risks caused by radon. She, too, is opposed to the parts of the proposal that permit coercive measures against property-owners, considering that the same time limit for measurements and remediation should apply to multi-family dwellings as to single-family dwellings, i.e. 20 years.

SSI's role in future anti-radon efforts

The Commission proposes bolstering SSI's official role. The Authority should continue to head the co-ordination group for agencies responsible for radon issues. The group's position should be strengthened and SSI's role clarified. SSI should retain its overall responsibility for issuing information about radon, and in collaboration with the other public agencies develop information material concerning radon. The Commission proposes that SSI also be responsible for establishing and running a 'radon portal' on the Internet. This portal should contain instructional and information material, as well as links to radon registers, the relevant agencies' websites, etc.

SSI should have the overall responsibility for training with respect to radon, and also have direct responsibility for training in health hazards and measuring technology. The National Board of Housing, Building and Planning is in charge of training in structural-engineering measures for both existing and newly erected buildings. The Geological Survey of Sweden (SGU) should be responsible for training with respect to soil radon. Course fees for municipal officers should be subsidised by the government. SSI should be responsible for developing Internet-based teaching material for a basic course about radon and introductory courses for special training programmes in measuring techniques, radon in water and structural-engineering measures to reduce high radon concentrations.

SSI needs to issue measurement protocols for radon in indoor air at workplaces and directions for selecting homes in carrying out measurements in multi-family dwellings. The measurement protocol for domestic radon levels needs reviewing. A standard method of measuring radon in drinking water needs establishing (a proposal has been submitted to the National Food Administration).

The Commission proposes making the National Land Survey and SGU responsible for radon registers for buildings, underground and water. The agency group for radon issues will determine the detailed configuration of the registers. The National Board of Health and Welfare will be responsible for collecting data on previous Rn measurements.

Two new positions for radon issues at SSI are proposed. One is needed for co-ordination and organisation of training activities. The other is necessary for management of the radon portal and administrative tasks stemming from the increase in the agency's radon-related activities.

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Advanced Techniques for the Determination of Solid State Uranium Speciation

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Abstract

Uranium released to the environment may be present in different physico-chemical forms, ranging from ionic species to particles and fragments. Following releases from nuclear events such as nuclear weapon tests or use of depleted uranium munitions, and from nuclear accidents associated with explosions or fires, uranium is predominantly present as particles, mainly fuel particles. To assess long-term impact from uranium contamination, information on the source term is essential, i.e. activity concentrations and isotopic ratios as well as the particle size distribution, crystallographic structures and oxidation states influencing particle weathering rates and the subsequent mobilisation and biological uptake. The activity concentrations, the isotopic ratios and the particle composition will depend on the source in question, while particle characteristics will also depend on the release scenario, dispersion processes and deposition conditions. Thus, the present paper focuses on advanced techniques such as mass spectrometry utilised for determination of uranium isotopic ratios, and on electron microscopy and synchrotron radiation based X-ray micro-techniques for characterisation of particles and solid-state speciation of uranium in particles. Results from research obtained during several years at the author's laboratory are presented to illustrate the usefulness of the techniques.

Introduction

To assess long-term environmental impact of actinide contamination including uranium (U), information on the source term is essential. Usually source term characteristics are restricted to inventory estimates, activity levels or activity concentrations of released or deposited actinides and other associated radionuclides. However, information on activity or isotopic ratios is essential to distinguish between multiple sources, for instance to distinguish U-particles associated with the use of depleted uranium munitions from U-particles originating from natural sources in the environment (Danesi et al, in press (a,b), Salbu et al., in press). Furthermore, information on speciation, including solid state speciation is essential for

assessing the mobility and bioavailability of actinides like U as well as associated radionuclides in various ecosystems (Salbu et al., 2000a).

A significant fraction of actinides including U released by high temperature nuclear events, such as nuclear weapons tests in Maralinga, Australia (Cooper et al., 1994), Mururoa, French Polynesia (Danesi et al., 1998), Nevada test site, US and Marshall Islands (Crocker et al., 1966;), or the use of depleted uranium (DU) munitions in Bosnia (Danesi et al, in press), and following the nuclear explosion in the Chernobyl reactor (Devell, 1986, Loschilov et al, 1992), or the fire in the Windscale nuclear reactor (Chamberlain and Dunster, 1958) is associated with fuel particles. U-particles have also been released under low temperature conditions such as atmospheric emission from the Windscale reactor during normal operations in the early 1950s (Jakeman, 1986; Salbu et al, 1994). Thus, man-made U particles have been released from nuclear sources more frequently than usually anticipated.

Particles containing actinides are formed due to critical or subcritical destruction of fuel matrices (e.g., explosions, fires, corrosion processes). Following high temperature accidental scenarios associated with nuclear installations (i. e. Chernobyl accident) a range of different uranium fuel particles has been observed, varying in composition, crystallographic structures (Salbu et al., 1998). Furthermore, the oxidation state of U in fuel particles depended on the release scenario; apparently reduced U were released during the explosions, while oxidised U from were released during the subsequent reactor fire (Salbu et al., 2000b; 2001). Following low temperature releases (i. e. pre-fire Windscale releases), however, flake-like uranium fuel particles significantly different from those collected at Chernobyl have been identified (Salbu et al., 1994). Therefore, the activity concentration and activity or isotopic ratios of matrix elements and refractory elements reflecting burn-up (e.g. lanthanides, actinides) are source-specific, while particle characteristics like crystallographic structures and oxidation states of matrix elements also depends on specific release conditions.

U particles represent point sources and the particle size distribution is essential for the potential of transfer to man via inhalation, as demonstrated for respiratory DU particles observed in Kosovo (Danesi et al., in press). After deposition in the environment, weathering of U-particles occurs and U as well as associated radionuclides are mobilised with time. Thus, the transfer of mobilised radionuclides within the ecosystem will be delayed until weathering takes place. The weathering rate will depend on the initial particle composition (e. g. UO_2 -fuel), structural changes occurring during the event (e. g. transformation from UO_2 to U_3O_8) and transformation processes taking place after deposition depending on soil pH, red/ox conditions and microbial activities (Kashparov et al, 1999). Unless the impact of particle weathering is taken into account, assessment of mobilisation, ecosystem transfer and long term consequences of radionuclide releases may suffer from large uncertainties. Thus, the present work focuses on analytical techniques applicable for determination of low level activity concentration of U to distinguish U isotopic ratios and on advanced techniques such as electron microscopy and synchrotron radiation based X-ray micro-techniques for characterisation of particles including solid state speciation of uranium in particles released from a source and deposited in the environment.

Analytical strategies –pre-analysis handling of samples

In environmental samples, U may be present in different physico-chemical forms, ranging from ionic species to particles. To obtain information on U species, different fractionation techniques must be applied during sampling *in situ*, at site or shortly after sampling and prior to analysis (Salbu,). To separate U-particles from air, cascade impactors with membranes having different cut-off levels (μm to mm) are frequently used. For U in waters, filtration ($0.45\ \mu\text{m}$) and tangential flow systems (nm to μm range membranes) should be applied to distinguish ionic species, colloidal and particulate material.

U particles represent a radioanalytical challenge as samples collected may not be representative of the bulk (Bunzl et al., 1997), sample dissolution may be incomplete (Oughton et al., 1993) and consequently contamination inventories may be underestimated. In contaminated areas portable detectors can be utilized to identify hot spots. For contaminated soils and sediments, biological material and filters from air or water fractionation procedures, autoradiography images are useful to locate radioactive particles. In autoradiography dried samples collected from hot spots are thinly spread on plastic foils and a radiation sensitive film is placed in close contact for varying time of exposure. Alternatively, phosphor image plating can be applied, being a more efficient technique, as demonstrated in Figure 1 for U particles released from the Chernobyl reactor. Hot spots reflect particles and further separations of subsamples using radiation detectors and light microscopes are needed prior to the use of EM-techniques.

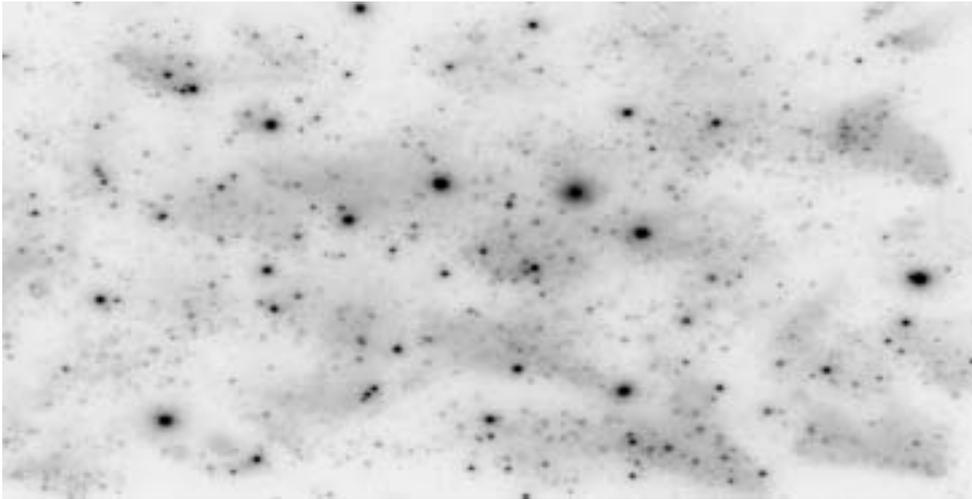


Fig. 1. Digital phosphor imaging of soil from within the 30-km zone to the west of Chernobyl.

Determination of low-level U and U isotope ratios by mass spectrometry

Prior to measurements, it is essential to obtain fully dissolutions of U in the samples (Oughton et al., 1993). Furthermore, radiochemical separations of U are usually needed to avoid interferences from other actinides. For the determination of very low concentration of specific actinide isotopes, and thereby isotopic ratios, different mass spectrometry systems using a variety of ion sources can be utilised. Among these are inductively coupled plasma (ICP-MS), thermal ionisation (TIMS), secondary ionisation sources (SIMS), and accelerator mass spectrometry (AMS); ICP-MS being most commonly used and AMS being most sensitive. During recent years, MS techniques have increasingly been applied to determination of U and actinides in environmental samples (e.g., Yamamoto et al., 1996)

Inductively coupled plasma emission - mass spectrometry (ICP-MS)

In ICP-MS, samples are introduced by means of a nebulizer, graphite furnace or by means of a laser (laser ablation). Although it is assumed that samples are fully ionised in the plasma (6000 - 8000K) before being transferred into the mass spectrometer particle discrimination may occur using nebulizer systems for sample introduction. By scanning the mass range within milliseconds, the ICP-MS, especially using sector instruments, acts as a sensitive multielemental technique (Becker et al., 1997). Thus, the isotopic ratios are utilised for source identification («fingerprint»). ICP-MS has proved useful for distinguishing between low-levels of nuclear weapon derived ^{239}Pu and nuclear fuel cycle derived ^{240}Pu (Oughton et al. 1999), while ICP-MS and SIMS have been successfully used to distinguish between depleted uranium particles and U originated from natural sources (Salbu, et al, in press, Danesi et al, in press (a,b)). By interfacing for instance chromatographic separation systems

(e. g., LC or HPLC) with ICP-MS, the combined system should be well suited for actinide speciation studies.

Accelerator mass spectrometry (AMS)

Among MS techniques, AMS offers almost unparalleled resolution, precision and ultra low-level detection limits (from 10^4 to 10^6 atoms). Prior to analysis, homogeneous solid metallic or metal oxide samples containing the actinide of interest together with a suitable isotopic tracer must be prepared. The ion source is produced by spluttering the solid sample with Cs^+ ions and injecting the negative ions into the accelerator. Then, the beam is accelerated towards a high voltage positive potential, stripped of outer electrons, accelerated as positively charged ions (up to 13+) and the isotopes are separated according to mass/charge in a high magnetic field before counting. The technique has been developed to enable measurement of actinides and has recently been applied successfully to measurement of $^{239}\text{Pu}/^{240}\text{Pu}$ isotope ratios in low-level environmental samples (Oughton et al., 1999). Thus, AMS represents a potential extreme sensitive technique for the determination of low-level U isotopes.

Characterisation of particles and colloids by electron microscopy

Transmission electron microscopy (TEM)

For colloidal radioactive material, transmission electron microscopy (TEM) can be utilised for structure and elemental analysis. For water samples, droplets are transferred to formvar coated grids and dried under an UV-lamp and electron dense structures can be recognised, when compared to blank (distilled water). By interfacing X-ray microanalysis (XRMA) elemental distributions can be obtained. Using TEM, colloidal material with particle sizes close to 20 nm and pseudocolloids in the range of 100 nm have been identified in effluents from La Hague, France and Sellafield, UK (Salbu et al., 2000a).

Scanning electron microscopy (SEM) and X-ray microanalysis (XRMA)

Following autoradiography and non-destructive radiation measurement techniques (e.g., gamma- and beta-spectrometry), individual particles can be localised using light microscopy and mounted on stubs, tape or capillaries prior to structure analysis by SEM and XRMA (Fig. 2a). Using Backscattered Electron Imaging (BEI) mode, bright areas reflect the presence of high atomic number elements on particle surfaces (Fig. 2b), while the distribution of elements is obtained by using X-ray mapping (Fig. 2c). XRMA provides also semi-quantitative information on the elemental composition on the particle surfaces (Fig. 2d). These techniques have been utilised to characterise different types of radioactive particles, e. g. flakelike uranium fuel particles released at low temperature conditions from Windscale, UK, and large aggregates of fuel granulates as well as crystalline and amorphous single fuel particles released at high temperature from the Chernobyl reactor (Salbu et al., 1994). Although all these particles are U-fuel particles, their behaviour in the environment is expected to be different; the transport of spheres are quite different from flakes, the weathering rates of amorphous structures are significantly higher than that of crystalline phases. Unless these processes are taken into account, model predictions on environmental behaviour such as soil-plant transfer may suffer from large uncertainties.

Synchrotron radiation (SR) based X-ray micro-techniques.

Following autoradiography, radioactivity measurements and electron microscopy, further particle characteristics are obtained by synchrotron radiation X-ray techniques using 2. generation synchrotron radiation source (e.g. HASYLAB, Germany) or 3. generation synchrotron radiation source (e.g. ESRF, France). The SR-based techniques include X-ray absorption (μ -XAS) tomography to determine the 3 D distribution of elements such as U, X-ray micro diffraction (μ -XRD) to determine the crystallographic structure and X-ray absorption near edge spectrometry (μ -XANES) to determine the oxidation state of U (Adams et al., 1998).

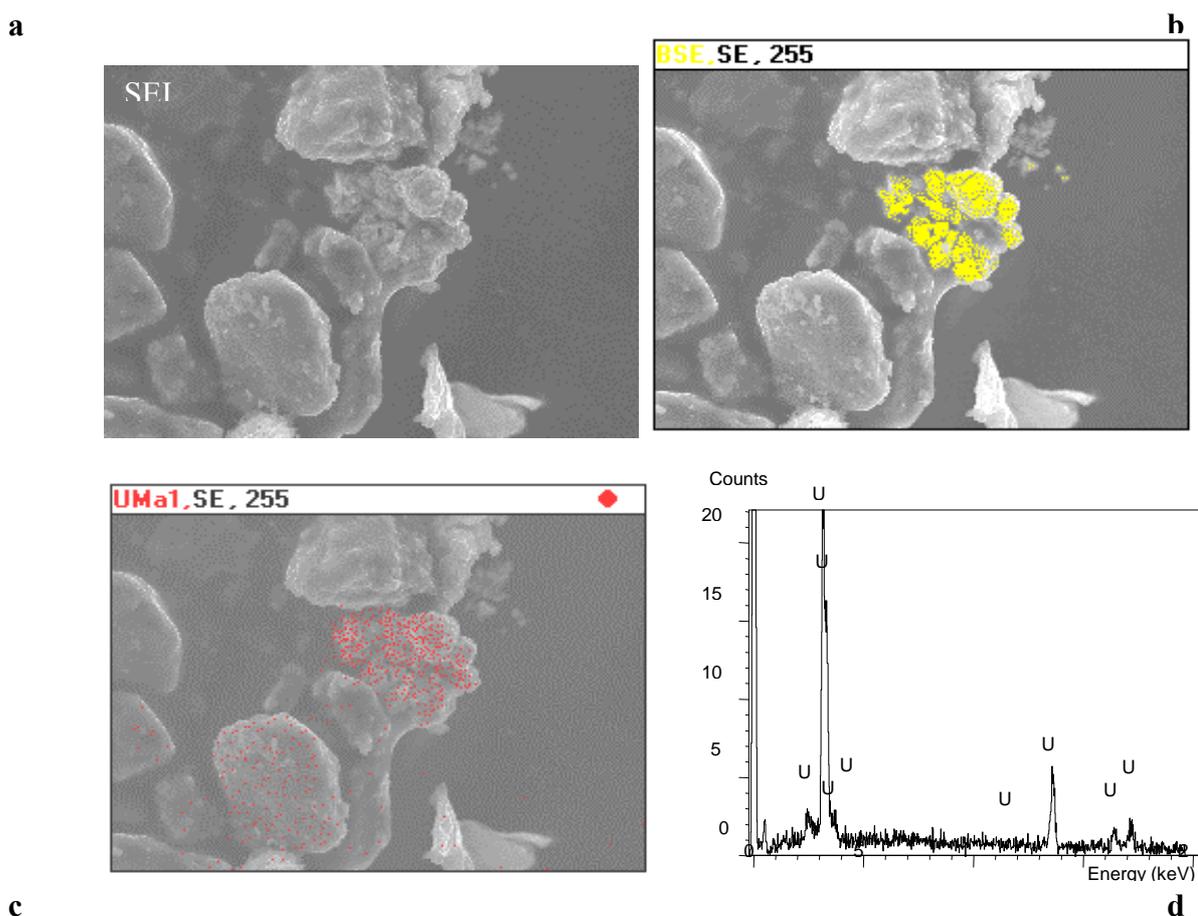


Fig. 2. Scanning electron microscopy of a depleted uranium particle from soils collected at the Ceja mountain, Kosovo: a) (upper left) Secondary Electron Imaging (SEI) mode reflecting the morphological structure of particles, b) (upper right) Backscattered Electron Imaging (BEI) mode, bright areas reflect high atomic number elements, c) (lower left) X-ray mapping of uranium in SEI mode d) (lower right) elemental analysis by XRMA. (Bar 100 μm).

Micro-tomography and micro-imaging

To obtain information on the 3 D distribution of U in individual particles, μ -XAS-tomography has been performed at ESRF (Salbu et al., 2000b). Each individual particle was mounted on a glass capillary and placed on a tomography stage with 8 degrees of freedom for alignment and rotation. The sample was rotated around a horizontal axis to obtain the highest resolution in the plane of reconstruction. During rotation, images were recorded at 17 keV with a high resolution, cooled CCD-based X-ray detector with a resolution of 0.6 μm . Monochromator tuning allows also images to be obtained as a function of incident photon energy to perform XANES imaging (2D oxidation state mapping). Using μ -XAS-tomography, the 3 D distribution of U in a fuel particle released during fire in the Chernobyl reactor is

shown in Figure 3. The tomographic reconstruction and computerised slicing of the 3-D image demonstrated that U was inhomogeneously distributed within the particles.

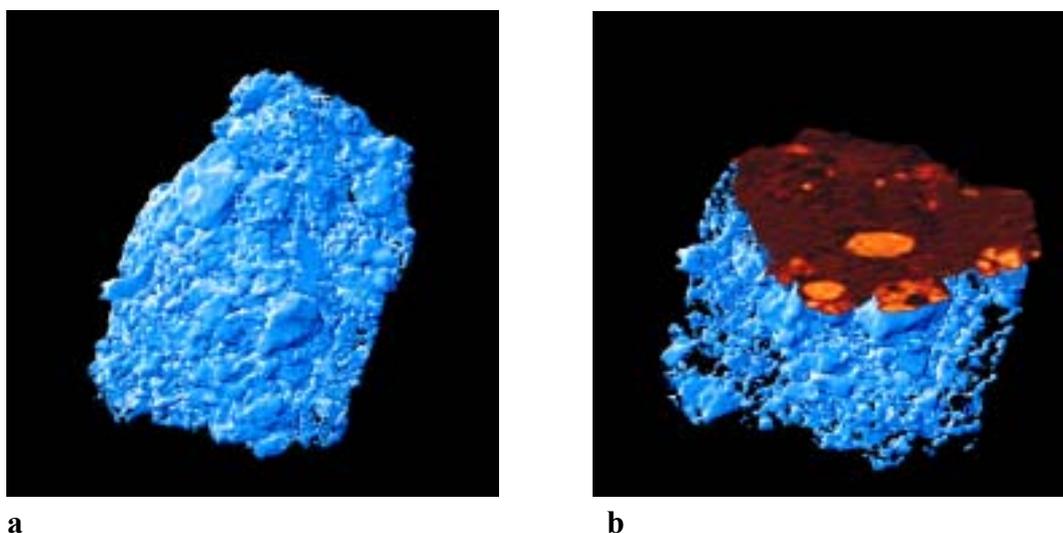


Fig. 3. a: μ -XAS-tomography of an oxidised fuel particle released from the Chernobyl reactor during the fire. **b:** computerised slicing of the 3-D image of the oxidised fuel particle (Salbu et al., 2001).

μ -XAS, μ -XRF, μ -XRD and μ -XANES

Information on the composition (μ -XAS, μ -XRF), crystallographic structure (μ -XRD) and oxidation states of elements (μ -XANES) contained in a particle on a submicrometer scale was obtained by using a high intensity X-ray microbeam; the hard X-ray radiation from the undulator passing through a Si monochromator was focused by a Fresnel Zone Plate to a spot of about 1.5 μm vertically and 5 μm horizontally on a sample at 0.7 m distance. The fixed exit double crystal monochromator allowed tuning of the energy over absorption edges, while keeping the beam position on the sample. The absolute flux at the beamspot on the sample was 10^9 photons/s at 17 keV. Long working distance optical microscope and high resolution X-ray CCD camera were used to position the sample in the focused X-ray beam. To calibrate the results obtained, standards well defined with respect to crystallographic structures and oxidation states were applied (U_{met} , UO_2 , U_3O_8 , and $\text{UO}_2(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$). The absorption spectra (μ -XAS, μ -XANES) were recorded with pindiodes, while the fluorescence (μ -XRF) spectra were recorded using a Si(Li) energy dispersive detector (Salbu et al. 2001).

μ -XRD

In micro-diffraction, the particles and standards were exposed for 3-10 min at different energies between 17 keV and 25 keV. Debye-Scherrer-rings were recorded at 200 mm distance from the sample using a Fujitsu image plate (Salbu et al., 2001). The plate was optically scanned with a Molecular Dynamics scanner to yield information on the diameter of the Debye-Scherrer-rings. The μ -XRD results demonstrated that U in the UO_2 fuel particles released from the Chernobyl reactor during the fire were oxidised to U_3O_8 or/and UO_5 .

μ -XANES

The μ -XANES spectra of particles and standards were obtained by scanning the X-ray energy over the U L_{III} absorption edge, and measuring the incident and transmitted beam intensity (I_0 , I) with pindiodes (Salbu et al., 2000b). By determining the inflection point energy as a function of photon energy for the standards, a correlation between the inflection point energy and oxidation state was established. By performing μ -XANES images, i. e. positioning the X-ray microbeam at various locations (pixels) across the particle and determining the inflection point of the XANES profile within each pixel, the 2D distribution of the oxidation state of U within the particles could be attained. As illustrated in Figure 4, a U particle released during the reactor fire was characterised by a UO_2 -core surrounded by oxidised U (U_3O_8 layers). In contrast, U particles released during the initial explosion was characterised by a UO_2 -core surrounded by apparently reduced U, probably due to interaction with carbon from the moderator (Salbu et al., 2001).



Fig. 4. 2 D μ -XANES imaging of an oxidised fuel particle released from the Chernobyl reactor during the fire. The particle has a UO_2 -core surrounded by an oxidised $\text{U}_2\text{O}_5/\text{U}_3\text{O}_8$ surface layer (Salbu et al., 2001).

Conclusions

To assess the impact of radioactive contamination for man and the environment, information on the source term including the physico-chemical forms is needed. To distinguish between U in man-made source from U originating from natural sources, the determination of isotopic ratio is essential. Being more sensitive than alpha-spectrometry, mass spectrometry techniques are highly useful for identifying sources (fingerprints). For very low levels of specific isotopes, AMS should be utilised.

As particle characteristics such as crystallographic structures and oxidation states influence the weathering and mobilisation of matrix elements as well as of radionuclides associated with radioactive particles, advanced techniques such as SEM and SR based X-ray micro-techniques are highly useful. As previously demonstrated, particle composition, size distribution and shape depend on sources in question, while the crystallographic structures and oxidation states of uranium in fuel particles released from the Chernobyl reactor depended on the release conditions. As these particle characteristics are essential for the environmental behaviour, the described advanced techniques should be utilised more frequently within radioecology providing information relevant for dose and impact assessments.

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Damage and Repair of DNA in Mammalian Cells – Emphasis on Oxidative Damage

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Abstract

The integrity of the genetic material, DNA, is continuously challenged by spontaneous decay, e.g. depurination leading to loss of bases, deamination leading to mutagenic base changes in DNA, damage from environmental chemicals, e.g. tobacco-specific nitrosamines, combustion products and drugs, as well as ultraviolet light and ionising radiation. Unless repaired, DNA damage may lead to inheritable disease, cancer and ageing. The major repair mechanisms are base excision repair, nucleotide excision repair, mismatch repair, recombinational repair and DNA end-joining. These mechanisms are integrated with other cellular processes such as cell cycle regulation, transcription and replication and even use some common proteins. Ionising radiation causes a wide range of base damage, as well as single strand breaks and double strand breaks in DNA. Proper handling of such damage requires several repair mechanisms, as well as other defence mechanisms.

Introduction

Genomes are damaged by environmental agents, spontaneous decay and replication errors (Lindahl, 1993, Lindahl and Wood, 1999, Krokan et al., 1997, 2000). Genetic changes cause inheritable disease, cancer and premature ageing. Ionising radiation cause base damage, as well as single strand and double strand breaks in DNA. These types of damage require different repair mechanisms. All cancer cells carry mutations in genes involved in growth control, and most are genetically unstable. More than 10^4 DNA lesions occur in each cell each day and defective DNA repair increases the risk of cancer (Lindahl, 1993). Furthermore, DNA repair is intimately integrated with cell cycle regulation, transcription and replication and use in part common factors. Some 130 human DNA repair genes have been identified (Wood et al., 2001), but the real number is possibly twice as high, since less than 50% of known and putative genes have an identified function. Adding genes involved in processes closely integrated with DNA repair probably increases the number of relevant genes several-fold. Only a fraction of these have been identified and even fewer studied at the functional level. Protein-protein interactions and essential protein modifications, e.g. phosphorylations, further increase the complexity of repair mechanisms.

The association between defects in DNA repair and cancer was established by James Cleaver in 1968. However, for approximately 25 years it was thought that only rare

syndromes, such as xeroderma pigmentosum (XP), Cockayne syndrome (CS) and ataxia teleangiectasia (AT) were associated with DNA repair defects (deBoer and Hoeijmakers, 2000). More recently, it has become clear that some of the most common hereditary forms of cancer are also associated with defects in DNA repair or processes integrated with and required for efficient DNA repair. These include hereditary nonpolyposis colon cancer (HNPCC), (Fishel et al., 1993) and early onset breast cancer (Cantor et al., 2001). In early onset breast cancer either *BRCA1* or *BRCA2* are mutated. These genes are required for repair of double strand breaks in DNA (Cantor et al., 2001, Khanna and Jackson, 2001). Thus, defects in the excision systems NER and MMR, as well as translesion synthesis (TLS) and DNA double strand break repair, are all associated with increased cancer risk. These observations have dramatically increased the general interest in DNA repair

Cells handle damage by two principally very different mechanisms; a) true repair mechanisms that restore DNA in an essentially error-free manner; and b) damage tolerance mechanisms, which may be either error-prone or error-free. In the latter, the damage is initially tolerated and bypassed by the replication machinery, and only repaired later. This mechanism includes recombination repair, which is essentially error free, and translesion synthesis (TLS) which is error prone. In TLS, recently discovered DNA polymerases copy the damaged DNA, but with reduced fidelity. This process is therefore error prone and mutagenic (Baynton and Fuchs, 2000). The true repair mechanisms include direct repair, excision repair and repair of double strand breaks (DSBs), by homologous recombination (HR) or non-homologous end joining (NHEJ). The best example of direct repair is demethylation of O⁶-methylguanine by O⁶-methylguanine-DNA methyltransferase (MGMT). This restores normal guanine in DNA in a one-step reaction in which the methyl group is transferred to a cysteine residue in MGMT, which thereby becomes enzymatically inactivated (Kaina et al., 2001). The excision repair mechanisms include base excision repair (BER), nucleotide excision repair (NER) and mismatch-repair (MMR). For all of these, the damaged strand is incised and a part including the damage removed. The complementary strand is then used for resynthesis of the missing segment in the damaged strand.

Nucleotide excision repair

Three known syndromes are associated with defects in NER; xeroderma pigmentosum (XP), Cockayne syndrome (CS) and trichthiodystrophy (TTD). These are all rare syndromes which have been comprehensively discussed elsewhere (deBoer and Hoeijmakers, 2000). Among these, only XP is cancer prone whereas the others cause developmental abnormalities and other phenotypic changes such as short stature. The NER pathway recognises lesions that cause major distortion of the DNA helix, such as pyrimidine dimers and benz(a)pyrene adducts (deBoer and Hoeijmakers, 2001). It may not have a role in repair of damage caused by ionising radiation. In NER, the damaged strand is cleaved on both sides of the lesion, releasing an oligonucleotide of approximately 30 nucleotides containing the damage. The gap is then filled and sealed. NER requires at least 25 polypeptides and two subpathways have been identified; global genome repair (GGR) and transcription coupled repair (TCR). In TCR, a transcription complex that has stalled at a site of damage in a strand undergoing transcription

is removed and factors involved in TCR are recruited. Two proteins, Cockayne syndrome protein A (CSA) and Cockayne syndrome protein B (CSB) are required for initiation of TCR, but not for GGR. Mutations in the genes for CSA or CSB cause Cockayne syndrome, which is characterised by deficient TCR, but proficient GGR. GGR does not require CSA or CSB. In GGR, damage is recognised by XPC in complex with HR23B. Subsequent steps are common for TCR and GGR. XP may be caused by mutations in at least 7 different genes (XPA through XPG) required for NER, giving rise to somewhat different phenotypes. In addition, an XP-variant (XP-V) exists, and this disease is not caused by NER but instead a defect in translesion synthesis (TLS) (Masutani et al., 1999, reviewed in deBoer and Hoeijmakers, 2001). In XP-V the gene for the moderately error prone DNA polymerase η (“eta”) (which can bypass thymine dimers) is inactivated by mutation. DNA polymerase η has the capacity to insert AA with relatively high fidelity when bypassing a thymine dimer. In XP-V its function is probably replaced by the much more error prone DNA polymerase ι (“iota”) which introduces mutations (Tissier et al., 2000).

Mismatch repair (MMR)

Mismatches in DNA occur mostly as a result of replication errors, especially in microsatellites containing repeats, e.g. dinucleotide repeats. A hallmark of defect in MMR is therefore microsatellite instability. In *Escherichia coli*, three proteins are uniquely involved in recognising the mismatch and initiating degradation of the DNA-segment containing the mismatched base or bases. These are MutH, MutS and MutL. Mammalian cells contain several homologues of MutH and MutL, but apparently not of MutS. Several other *Escherichia coli* proteins, also used for other purposes, are required to complete MMR. Hereditary non-polyposis colon cancer (HNPCC) in man is caused by mutations in genes for mismatch repair (MMR), most commonly in the genes *hMSH2* (45%), *hMLH1* (45%) and *hPMS1/2* (10%). Furthermore, mutations in these MMR-genes are also observed in 10-12% of sporadic colon cancers, the significance of which is not yet known. MMR is not thought to be involved in repair of damage induced by ionising radiation (Jiricny et al., 2000).

Base excision repair (BER)

The last of the excision repair systems, BER, is now reasonably well understood as far as genes/proteins involved and mechanism of repair is concerned (Figure 1). Although BER probably is responsible for repair of a majority of cellular DNA damages (reviewed in Lindahl, 1993, Krokan et al., 1997, 2000), the functional significance of BER in prevention of disease remains unclear. The BER-pathway is the main mechanism for removal of endogenous DNA lesions that cause minor helix distortions (Lindahl 1993). In addition, BER is required for repair of similar types of base damage caused by environmental agents, such as alkylations from nitrosamines and base damage from ionising radiation. Endogenous sources of damage include DNA damage caused by hydrolytic processes, such as hydrolytic

deamination of cytosine, adenine and guanine and hydrolytic base loss (mostly purines), oxidation by reactive oxygen species (e.g. hydroxyl radicals), as well as endogenous alkylating agents such as S-adenosylmethionine (SAM), (Krokan et al., 1997, 2000).

The BER pathway is initiated by non-enzymatic base loss, or by a DNA glycosylase. Each DNA glycosylase is specific for a limited number of damaged bases (Krokan et al., 1997, 2000, Lindahl and Wood 1999). DNA glycosylases are either monofunctional and remove the base only, leaving an intact abasic site (e.g. uracil-DNA glycosylase and alkylpurine-DNA glycosylase), or are bifunctional because they in addition to the glycosylase activity have a lyase activity, which cleaves DNA 3' of the abasic site (AP-site). At least 8 different human DNA glycosylases have been identified (Table I). Subsequent to base removal, repair is completed by short patch repair (one nucleotide gap), or long patch repair (2-8 nucleotide gap), (Pascucci et al., 1999, Matsumoto et al., 1999). These mechanisms largely use different enzymes and accessory proteins (Fig. 1).

Table 1. Human DNA glycosylases identified

<u>Name</u>	<u>Lyase</u>	<u>Localization</u>	<u>Chrom.</u>	<u>Preferred substrates</u>
hUNG1	No	Mitochondria	12q24.1	Uracil (ssDNA>dsDNA)
hUNG2	No	Nuclei	"	"
hSMUG1	No	Nuclei?	12q13.1-q14	5OH-MeUracil and Uracil
hTDG	No	Nuclei	12q24.1	U:G>εC:G<T:G
hMBD4	No	Not known	3q21	U or T in U/TpG:5meCCpG
hMPG	No	Nuclei/mit?	16p (tel)	3meA, 7MeA, 3meG, 7meG, 8-oxoG, hpx, εA, εG, A,G
hOGG1	Yes	Nuclei/mit	3p25	Me-fapyG:C>fapyG:C>8oxoG:C> 8oxoG:T
hMYH	Yes?	Nuclei/mit	p32.1-p34.3	A:G, A:8oxoG (removes A)
hNTH1	Yes	Nuclei (+mit?)	16p13.2-13.13	T/C-glycol, dihydrouracil, fapy

The steps involve formation of a single stranded gap, filling of the gap by DNA synthesis, and ligation. The choice of pathway is at least in part determined by the nature of the DNA glycosylase (Fortini et al., 1999) and the nature of the resultant AP-site, but may also depend on the timing in the cell cycle and subnuclear localisation of the process (Otterlei et al., 1999). Thus, the long patch pathway requires a number of factors that are also used in DNA replication, such as DNA pol δ or ε (apparently stimulated by DNA pol β) FEN1, PCNA, DNA ligase 1 and possibly RPA (reviewed in Krokan et al., 2000). At least for removal of misincorporated uracil, the repair process takes place in replication foci (Otterlei et al., 1999) and results from mice with targeted deletion in the *Ung*-gene strongly implicates the Ung-protein in this process (Nilsen et al., 2000). Short patch repair does not require PCNA or FEN1 and uses DNA polymerase β and DNA ligase III stimulated by XRCC1 (Kubota et al., 1996). This information is largely derived from successful *in vitro* reconstitution experiments in a number of laboratories with purified factors or cell extracts (for a methods description, see Frosina et al., 1999).

The choice of pathway may be of special importance for repair of oxidised bases, as these often appear in clusters in combination with strand breaks. Interestingly, the known

glycosylases directed against oxidised bases are all bifunctional. Thus the DNA backbone is cleaved 3'- to the AP-site, and the baseless sugar is retained on the 3'- end and subsequently removed by HAP1 or Pol β . The lack of an 5'-dRP end apparently prevents 5'-3' strand displacement during the polymerisation step, and occurs via single-nucleotide insertion. This mechanism avoids polymerisation across neighbouring strand breaks, which otherwise would have resulted in a double-strand break.

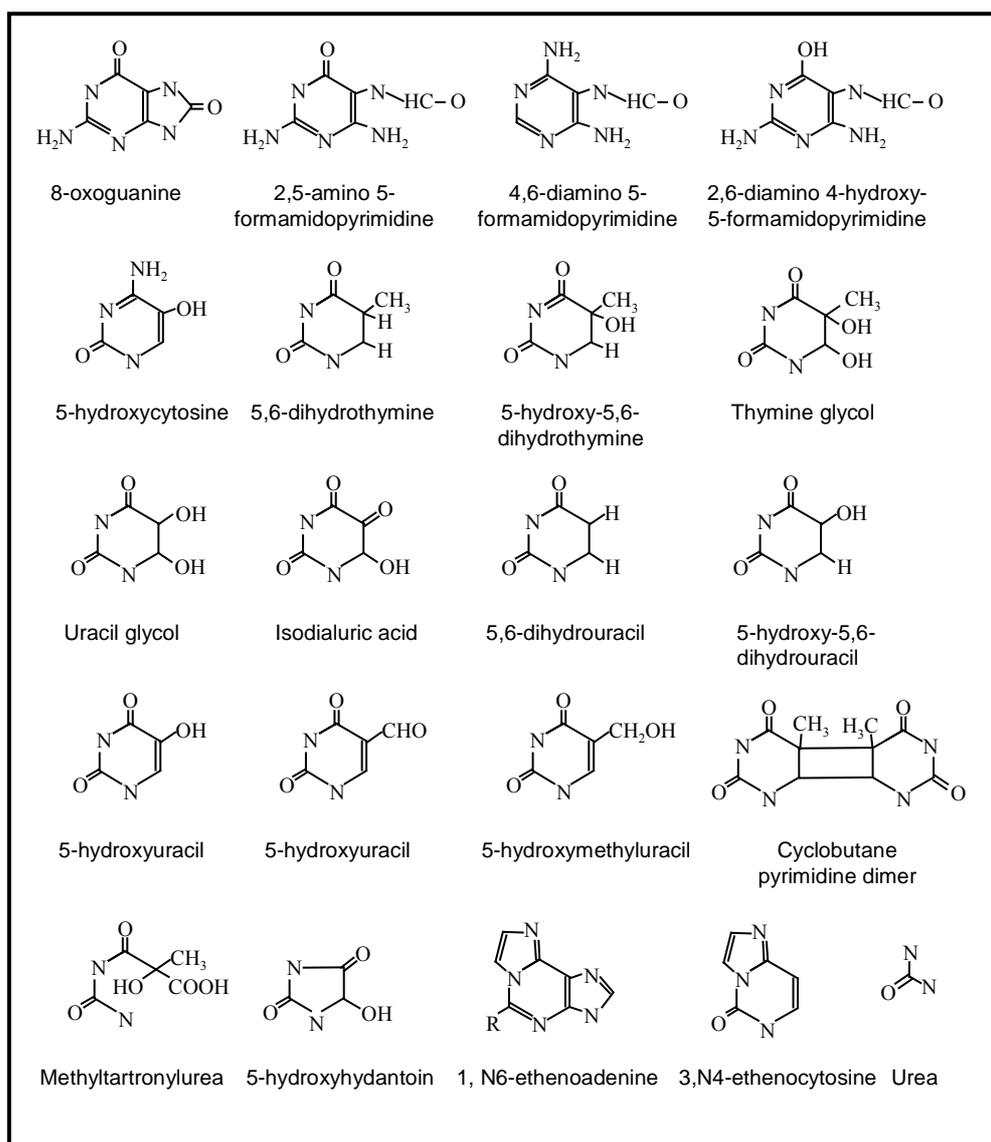


Fig. 1

While the large number of damaged bases from endogenous sources and the high conservation of the BER pathways suggest an important role for BER in maintenance of the DNA integrity, the significance of BER in prevention of disease is still not known. So far,

search for inactivating mutations in BER-enzymes in human disease has given some indications on mutations in BER-proteins in cancer, but unlike other repair deficiencies no distinct condition has so far been associated with defective BER. Possibly an association with one distinct condition would be unlikely, considering the wide range of damage that is repaired by BER. DNA pol β mutants have been identified and may be associated with lung cancer (Bhattacharyya et al., 1999). Furthermore, dominant negative mutants of DNA pol β have been identified in human cancer (Bhattacharyya and Banerjee, 1997). Unfortunately, these interesting results appear not to have been followed up in new or expanded studies. As described below, mutations in the gene for 8-oxoguanine-DNA glycosylase (hOGG1) may also be associated with cancer. In addition, promoter mutations in the *UNG*-gene so far only observed in cancer cells have also recently been reported. Mutations/allelic variations in the human *UNG*-gene have also been reported, but are not specific to cancer cells (Kvaløy et al., 2001). Thus, while mutations in the BER genes may not be common, subtle yet important BER-defects at the regulatory levels may be more common. This may include unbalanced expression of BER-proteins (reviewed in Frosina 2000), incorrect post-translational modification or processing (not studied) and disrupted intracellular transport. Disrupted subcellular localisation of AP-endonuclease (HAP1) was reported to be quite frequent in colon cancer (Kakolyris et al., 1997) as well as in lung cancer, where nuclear localisation is associated with better prognosis (Kakolyris et al., 1999). In the present study we want to expand our studies on possible deficiencies in BER, including imbalanced expression and abnormal post-translational modification of various factors.

Repair of damage induced by ionising radiation and oxidative stress by BER, homologous recombination (HR) and non-homologous end joining (NHEJ)

Damage to DNA by ionising radiation or oxidative stress comprises oxidative damage to bases, sugar and single strand or double strand breaks in DNA. In addition, adjacent single strand breaks in opposite strands may be converted to double strand breaks upon replication. DSBs are lethal unless repaired. Base damage may be mutagenic, cytotoxic or both. DNA may be damaged due to direct hits from the ionising rays, or as secondary damage from radicals generated by the radiation. The generation of these is outlined in Table 2.

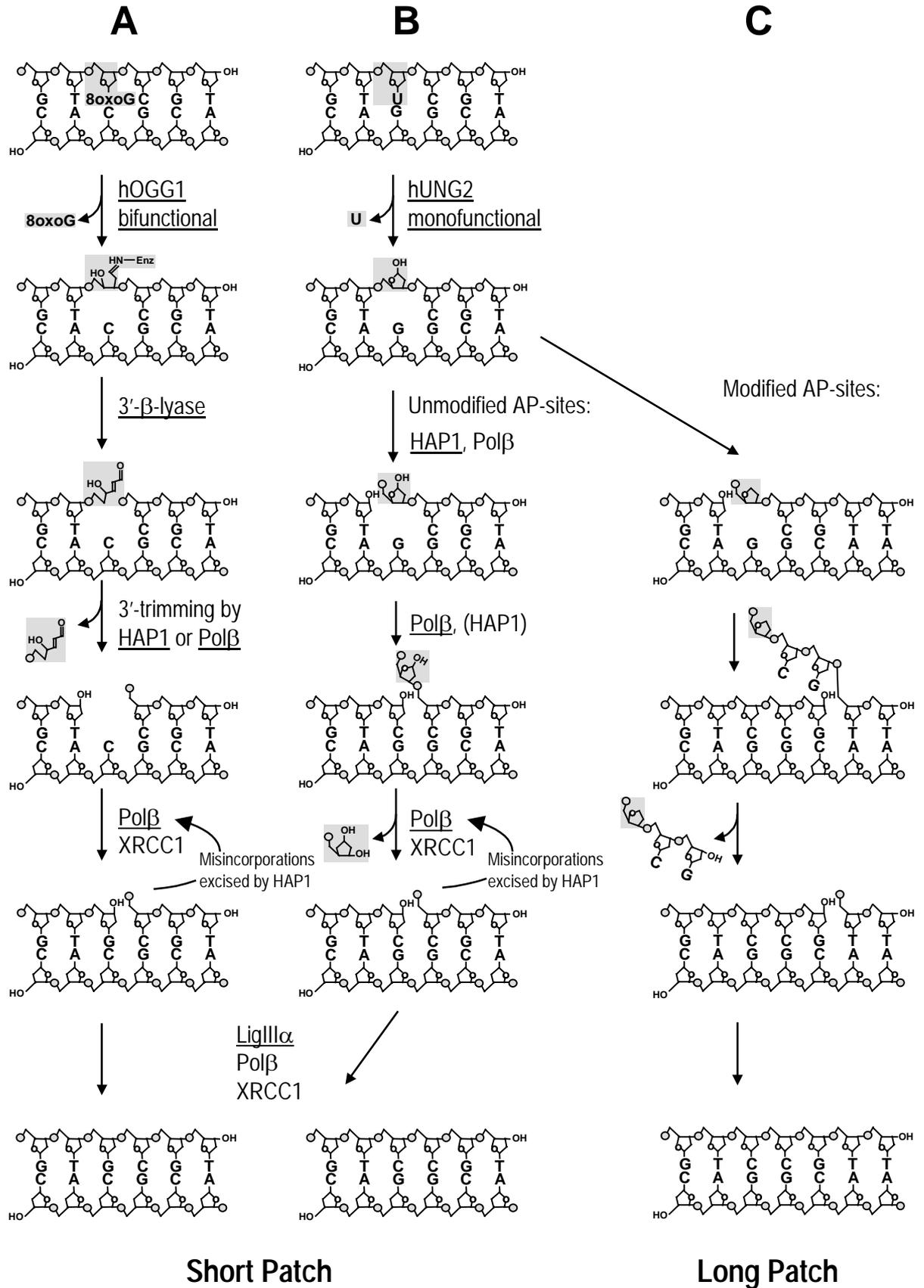


Fig. 2. A wide range of oxidised and ring-fragmented nitrogen bases are formed by endogenous reactive oxygen species (ROS) or by ionising- or UV-radiation.

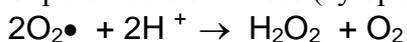
Table 2. Formation and deactivation of reactive oxygen species (ROS)

Generation of ROS:

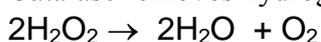
1. $\text{H}_2\text{O} \rightarrow \text{H}_2\text{O}^+ + \text{e}^-$
2. $\text{H}_2\text{O}^+ + \text{H}_2\text{O} \rightarrow \bullet\text{OH} + \text{H}_3\text{O}^+$ Hydroxyl radical
3. $\bullet\text{OH} + \bullet\text{OH} \rightarrow \text{H}_2\text{O}_2$ Hydrogen peroxide
4. $\text{e}_{\text{aq}}^- + \text{O}_2 \rightarrow \bullet\text{O}_2^-$ Superoxide radical
5. $2 \text{O}_2^- + 2 \text{H}^+ \rightarrow \text{O}_2 + \text{H}_2\text{O}_2$

Protection against ROS:

Superoxide dismutases (cytoplasm and mitochondria):



Catalase removes hydrogen peroxide:



Induction and repair of oxidative base damage

The mechanism of induction of damage, as well as structural changes in bases after exposure to oxidative stress have been comprehensively reviewed recently (Dizdaroglu, 1999). More than 20 different types of base damage after exposure to oxidative stress have been identified. Most of these are shown in figure 2. Repair of base damage, when known, is by the BER route. The most prevalent damage to purines is 8-hydroxyguanine, or more commonly named 8-oxoguanine, while the most common damage to pyrimidines is the formation of thymine glycol. The mechanism of induction of base damage involves the action of free radicals and other reactive oxygen species (ROS). These are generated when water is ionised by the radiation. Enzymatic mechanisms to detoxify ROS also are present in cells and constitute a primary defence (Table 2). Furthermore, enzymatic hydrolysis of oxidised purine nucleoside triphosphates such as 8-oxo-dGTP, 8-oxo-dATP avoids errors caused by their misincorporation during DNA replication (Sakai et al., 2001). Repair of DNA damage caused by ROS is a secondary defence mechanism. In the case of 8-oxoguanine a hydroxyl radical, which is highly reactive, first reacts with guanine to form a C8-OH-adduct radical. Then the loss of an electron (e^-) and proton (H^+) generates 8-oxoguanine. The C8-OH-adduct radical may also be reduced by uptake of an electron and a proton forming 7-hydro-8-hydroxyguanine which is subsequently converted to 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FaPy), a second major oxidation product of guanine (Dizdaroglu, 1999). Generation of oxidised pyrimidines, such as thymine glycol, also results from radical attacks. First, reaction with a hydroxy radical yields 5-hydroxy-6-yl-radical. In the absence of oxygen, loss of an electron followed by uptake of water and loss of a proton generates thymine glycol. In the presence of oxygen, uptake of oxygen at position 6 first yields a 5-hydroxy-6 peroxy radical which is converted to thymine glycol through loss of a proton and $\text{O}_2\bullet^-$ and reaction with water. Several uracil-analogues are generated from cytosines after

exposure to ionising radiation or ROS from other sources. These analogues include, among others, alloxan, isodialuric acid and 5-hydroxyuracil (Fig. 2).

Studies on repair of base oxidative base damage have so far concentrated on major products, all of which are repaired by BER. 8-oxoguanine in the template may lead to GC→TA transversion due to the altered base-pairing properties of 8-oxoguanine (Lindahl, 1993, Lindahl and Wood, 1999). Mutations in the gene *hOGG1* that encodes an 8-oxoG-DNA glycosylase (Audebert et al., 2000a) as well as loss of heterozygosity (LOH) at this locus (Wikman et al., 2000) have been associated with lung cancer. Furthermore, missense mutations have been identified in approximately 4% of clear cell carcinomas of the kidney (Audebert et al., 2000b). The studies on the mutations in the *hOGG1* gene and association with various cancer forms (lung, kidney) possibly represent the strongest link between BER and cancer so far. hOGG1 comes in seven splice forms (Nishioka et al., 1999), although two (hOGG1-1a and hOGG1-1b) are the most abundant forms at the transcript level (Arai et al., 1997). hOGG1-1a is a nuclear protein and hOGG1-1b mitochondrial. hOGG1 is a bifunctional glycosylase that removes 8-oxoguanine, as well as FaPy, and cleaves the damaged strand 3' of the deoxyribose resulting from the glycosylase activity. hOGG1 removes 8-oxoguanine and FaPy residues with the highest efficiency when in pair with cytosine, and is followed by strand cleavage via beta-elimination. However, significant removal of 8-oxoG from mispairs (8-oxoG: T >G >A) is also observed, but essentially without an associated strand cleavage. Interestingly, assays with abasic site DNA showed that strand cleavage was dependent on the presence of C in the opposite strand, irrespective of the prior removal of an 8-oxoG residue. Thus strand incisions are made only if repair completion results in correct base insertion, whereas excision from mispairs preserves strand continuity and hence allows for error-free correction by a postreplicational repair mechanism (Bjørås et al., 1997). If an 8-oxoguanine in the template generated by an oxidative attack results in incorporation of dAMP during replication, the human MutY homologue hMYH removes adenine, thus initiating the BER process which may (or may not) result in incorporation of the correct nucleotide, dCMP. If the incorrect dAMP is again incorporated, the cycle may if necessary be repeated until dCMP is incorporated. Oxidative stress may also oxidise dGTP to 8-oxodGTP, which can be misincorporated opposite of adenine in the template strand. This potential misincorporation is minimised by an 8-oxodGTPase (in *E. coli* MutT) which efficiently degrades 8-oxodGTP to 8-oxodGMP. The human orthologue is called hMTH1 (human MutT homologue 1). Thus, the cell prevents 8-oxoguanine-induced mutations both at the DNA level by DNA glycosylases (hOGG1 and hMYH) and the dNTP level (hMTH1). In addition, it has been demonstrated that other mechanisms contribute to removal of 8-oxoguanine in DNA. Thus, it has been demonstrated that the removal of 8-OxoG in a wild-type mouse embryonal fibroblast (MEF) cell line is faster in the transcribed strand (TS) than in the non-transcribed strand (NTS), indicating TCR of 8-OxoG in murine cells. Furthermore, in a MEF cell line from a gene targeted mouse deficient in *Ogg1* (*ogg1*(-/-)), 8-OxoG was not removed from the NTS whereas there was still efficient 8-OxoG repair in the TS. Introduction of *Ogg1* protein in the *Ogg1*-deficient cell line restored the ability to remove 8-OxoG in the NTS. Thus, TCR is involved in removal of 8-oxoguanine from the TS, but not in the NTS (La Page et al., 2000a). This backup system may explain the lack a mutagenic phenotype of

knockout mice deficient in Ogg1-activity (Klungland et al., 1999). TCR of 8-oxoguanine has been demonstrated to require XPG, TFIIH, and CSB proteins. Furthermore, defective TCR results in enhanced mutation frequencies at 8-oxoguanine. In addition, 8-oxoguanine also blocks transcription by RNA polymerase II and this may be the signal required for release of the polymerase and recruitment of repair factors (La Page et al., 2000b).

Oxidised pyrimidines, such as thymine glycol are also repaired by BER. Thymine glycol and some related bases are removed by the bifunctional DNA glycosylase hNTH1, a homologue of bacterial Nth (Eide et al., 2001). Interestingly, XPG strongly stimulated removal of thymine glycol by hNTH1, demonstrating yet another function of XPG. The XPG protein stimulates the binding of HsNTH protein to its substrate and increases its glycosylase/AP lyase activity by a factor of approximately 2 through direct interaction between the two proteins (Bessho, 1999). Several oxidised cytosines, e.g. isodialuric acid, 5-hydroxyuracil and alloxan, have structures resembling uracil and are in fact removed by human uracil-DNA glycosylase from the *UNG* gene (Dizdaroglu et al., 1996). Although the rate of removal of these derivatives is slow compared with the preferred substrate, uracil, it is approximately as fast as the removal of various oxidised substrates by other DNA glycosylases (Krokan et al., 1997). However, the possible physiological significance of UNG-protein in removal of oxidation products remains to be determined.

Table 3. Ataxia teleangiectasia: increased sensitivity to ionising radiation

Characteristics:

- Incidence 1 in 300,000, autosomal recessive
- Progressive cerebellar ataxia, teleangiectasies, immune deficiency
- High risk of lymphoma or leukemia
- Increased sensitivity to ionising radiation
- Heterozygotes (1 in 550) have increased risk of cancer, especially in breast

Genetics:

- *ATM* gene in 11q22-23 mutated, large gene, 66 exons, > 300 mutations known
- 4 complementation groups, but all mutated in the *ATM* gene
- Several chromosomal aberrations in AT (chromatid gaps, breaks, translocations)
- Normal ATM-protein senses double-stranded DNA breaks, activates cell cycle check points and modulates several processes, also involved in meiosis

Repair of double strand breaks by homologous recombination (HR) and non-homologous end joining (NHEJ)

Double strand breaks (DSBs) are generated by a variety of genotoxic agents, including ionising radiation and radiomimetic chemicals. In addition, they can be generated when advancing DNA replication complexes arrive at single stranded breaks in the template. They are also generated as intermediates during certain site-specific recombination processes (reviewed in Jackson, 2001). A single unrepaired cellular DSB can result in cell death, thus their repair is very important. Mammalian cells deal with DSB using several mechanisms. These include signalling of damage, repair by at least two different systems, cell cycle arrest, apoptosis and apparently adaptive survival responses.

In mammalian cells, the repair of DNA double-strand breaks (DSBs) occurs by both homologous and non-homologous mechanisms. Several articles and reviews have suggested that NHEJ is much more frequent than repair by HR. However, the mechanism of repair may be cell cycle-dependent. Thus, more recent research indicates that HR may be the predominant mechanism after completion of the S-phase when an identical copy of the DNA strand, the sister chromatid, is available. In G₁, only the homologous chromosome is available and this may be harder to find, thus NHEJ may be the preferred mechanism of repair in G₁ (reviewed in Hoeijmakers, 2001, Pastink et al., 2001). The sister chromatid is apparently preferred 2-3 orders of magnitude to a homologous or heterologous chromosome (Johnson and Jasin, 2001). Whereas HR is essentially error free, NHEJ may involve loss or gain of a few nucleotides.

HR and NHEJ are very different mechanisms and they require largely different protein factors. However, both require the ATM-protein encoded by the *ATM* gene for damage recognition and probably for recruitment of repair factors. Inactivating mutations in *ATM* cause ataxia teleangiectasia, a rare syndrome characterised by highly increased sensitivity to ionising radiation, cerebellar degeneration, teleangiectasias, increased cancer risk and immunodeficiency (Table 3). ATM and ATR (ataxia teleangiectasia related protein) are very large protein kinases which together with DNA-PK_{cs} are required for phosphorylation of histone H2AX in the DNA domain next to the DSB over a distance of a megadalton. This phosphorylation takes place within 1-3 min after damage induction and may produce a chromatin state required for repair. H2AX rapidly forms nuclear foci at the break site and RAD50, RAD51 and BRCA1 are later recruited to such foci (Paull et al., 2000).

In HR the complex RAD50/MRE11/NBS1 has a 5'-3' exonuclease activity that digests several nucleotides from both strands, preparing DNA for strand invasion (Fig. 3), (Hoeijmakers, 2001). RPA may promote assembly of RAD51 (a RecA homologue) nucleofilament on the protruding ends. The nucleofilament may also include the related proteins XRCC2, XRCC3 and RAD51B, C and D. RAD52 stimulates the assembly. RAD54, a DNA-dependent ATPase that interacts with RAD51, has been shown to induce supercoiling and may stimulate recombination indirectly by displacing histones and/or other proteins packaging the DNA into chromatin (Ristic et al., 2001). This process also requires BRCA2 that may be involved in nuclear translocation of RAD51 and BRCA1. Having set up the damaged DNA for strand invasion, an intact double stranded sister chromatid is identified and is used as template for copying damaged regions by DNA synthesis from broken ends. The Holliday junctions are resolved by resolvases, and the process completed by ligation (Hoeijmakers, 2001).

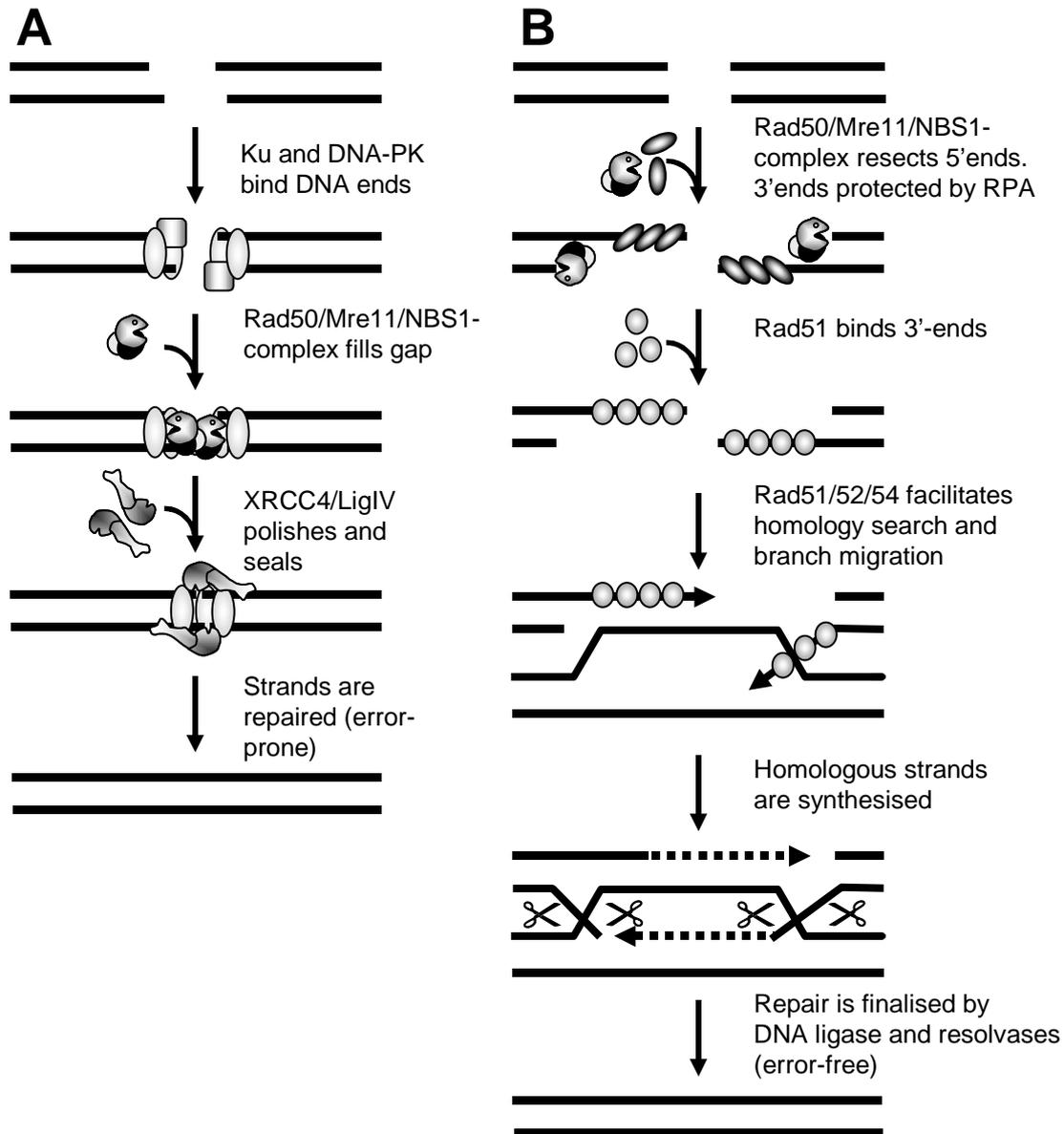


Fig. 3. Mechanisms of DSB repair. A: In non-homologous end-joining the two ends are rejoined directly by end-binding protein heterodimer Ku70/80 and DNA-PK_{CS}. XRCC4/ligase4 covalently seals the break. DNA-ends that require processing before ligation, are digested by the Rad50/Mre11/Nbs1-complex, and generally result in minor deletions in the DNA. B: Homologous recombination is less understood, but involves digestion of the 5'-ends and formation of a 3'-nucleoprotein filament containing Rad51/52/54 and accessory proteins. This filament invades a homologous sequence of a sister-chromatid, which is then used as a template for proper healing of the broken ends by DNA-synthesis. Finally, the so-called Holliday-junction is resolved by resolvases.

NHEJ is apparently the preferred process in G1 cells in which no sister chromatid is available. As mentioned, the homologous chromosome is inefficiently used in HR, relative to the sister chromatid. In template-independent repair by NHEJ, the ends of DSB are joined,

but not without frequent errors in the form of loss or gain of a few nucleotides. NHEJ requires the KU70-KU80 complex that binds to the broken ends. KU70 and KU80 are regulatory subunits of DNA-dependent protein kinase (DNA-PK) which also contains a 460-kDa catalytic subunit (DNA-PK_{CS}). Exactly how the complex functions in NHEJ is not clear, but one role is presumably to approximate the ends and to protect them from degradation. DNA-PK also has other functions, e.g. S-phase checkpoint arrest following irradiation. Ligation is carried out by the XRCC4-Ligase4 complex (Hoeijmakers, 2001).

In conclusion, repair of DSBs in DNA is starting to become understood, although the information on the proteins involved and their mechanisms of action are far from complete. Many proteins are conserved from bacteria to man, but the repair process is much more complicated in man than in bacteria, e.g. many homologues of bacterial RecA are present in mammalian cells. Given the importance of repair of DSB in prevention of cell death, as well as prevention of cancer development it should be a matter of high priority.

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Low-dose hypersensitivity and adaptive responses to radiation.

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Adaptive response as induced by a small priming radiation dose

The term adaptive responses to ionizing radiation usually means that the cellular sensitivity to a dose of radiation decreases if the cells are given a small radiation dose (5-40 cGy) a few hours prior to irradiation (Olivieri *et al.* 1984; Skov 1999a). In some reports priming has been observed even at lower radiation doses and with negative correlation to the priming dose (Cai and Liu 1990). The priming radiation dose protects not only against subsequent irradiation, but also against subsequent treatment with DNA-damaging chemicals (Wolff *et al.* 1988; Wolff 1992; Caney *et al.* 1999). The priming dose obviously activates processes in the cells that tend to change their sensitivity to a subsequent radiation dose. It has been reported that small radiation doses at the dose level which induces priming, involve increased DNA-repair (Ikushima *et al.* 1996), but also induction of several stress genes in p53-competent cells (Amundson *et al.* 1999) and repression of a gene which is not repressed by high radiation doses (Robson *et al.* 1999).

Adaptive responses have been seen with several types of endpoints, like chromosomal aberrations (Olivieri *et al.* 1984), cell survival (Shadley and Dai 1992; Marples and Joiner 1995). and carcinogenesis (UNSCEAR 1994).

Different laboratories have presented different data for adaptive effects. This is probably due to variations between different cell lines concerning adaptive responses (Raaphorst and Boyden 1999). In a recent paper Raaphorst and Boyden (1999) report that the adaptive response does not seem to be related to cell radiosensitivity or to whether or not cells originate from normal or from cancer tissue.

The adaptive response is obviously depending on protein synthesis. Following the priming dose, it takes several hours before a significant adaptive effect can be observed (Shadley *et al.* 1987), and if protein synthesis is inhibited with cycloheximide, no adaptive effect is seen (Youngblom *et al.* 1989).

Low-dose hypersensitivity and induced radio-resistance.

These terms refer to the observation that cell survival is more reduced per dose increment for small radiation doses (less than 50 cGy of X- or γ -rays) than for larger doses. On a dose response curve there is a steep initial slope, followed by a flat region (or in some cases even an increased survival with increasing dose over a small dose region), then a shoulder and a subsequent steeper region (Marples and Joiner 1993, Lambin *et al.* 1993) (Fig. 1). This means that radiation response to acute irradiation is dose dependent, with a hypersensitive region for doses below about 20 cGy and lower sensitivity for larger doses. In other words, small acute doses (below about 20 cGy) are more lethal per absorbed energy unit than larger doses.

This effect is not due to variations of radiation response of cells in different phases of the cell cycle (Marples and Joiner 1993; Lambin *et al.* 1994; Short *et al.* 1999, Chadwick and Leenhouts 1998 and Wouters and Skarsgard 1998). The low-dose hypersensitivity is overcome by a priming dose of 0.05 to 1 Gy given 6 hours prior to the challenge dose (Marples and Joiner 1995). It is also overcome if the cells are given a pre-treatment with hydrogen peroxide (Marples and Joiner 1995). A standing theory is that the adaptive responses operate via reactive oxygen species (Feinendegen 1999). It probably involves repair of DNA and that protein synthesis is needed, since the effect is counteracted if the protein synthesis inhibitor cycloheximide is present during a 6 hours interval between doses (Marples and Joiner 1995).

The variation in radiosensitivity in various phases of the cell cycle is seen in the part of the cell survival curve above 50cGy (Skarsgard *et al.* 1994).

Adaptive response versus hormesis

There has been some confusion about the two terms adaptive responses and radiation hormesis. These terms are not synonymous.

Adaptive responses relate to an increased ability of cells and organisms to resist radiation damage following a priming radiation dose. Still, the well-being of the cells is not better after the primary dose than before the irradiation.

With radiation hormesis, however, the response is different. By a hormetic effect most researchers mean that the cell or organism appear to have improved, for example in growth, survival or some other characteristics after low-level radiation as compared to the situation before. (Mossman and Ledesma 1999). Hormesis might, for example, improve the activity of the immune system during its recovery from a small radiation dose (Macklis and Beresford 1991). It can even be argued that an adaptive effect may entail hormesis although this is not necessarily so (Feinendegen 1999). Induced radioresistance, as observed by the change of slope of the dose response curve at doses above 5-40 cGy, is probably not the effect of hormesis (Skov 1999b).

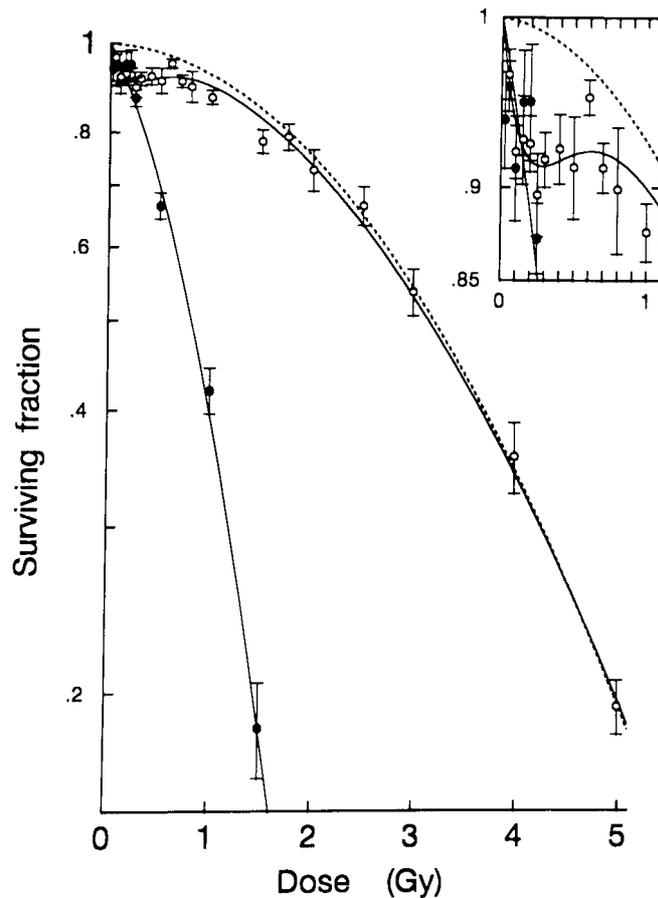


Fig. 1. Cell survival of Chinese hamster lung cells, V79, as measured by cells ability to form macroscopic colonies following radiation with 240 kVp X-rays and d(4)-Be neutrons (closed symbols). The lines represent fits to the data of mathematical models. (From Lambin *et al.* 1993)

A problem with the term hormetic effect, using this interpretation, is that all organisms are under constant background irradiation. Although this radiation level is usually very low, it is not zero. All organisms may, therefore, experience a hormetic effect even at the ordinary background level of irradiation.

Is it possible to explain how low-dose radiation can protect against cancer?

Large radiation doses (i.e. >50-100mSv) undoubtedly have carcinogenic effects (e.g. Thompson *et al.* 1994), although such effects are much smaller than most people seem to believe. The excess relative risk, meaning the ratio of the cancer frequency between exposed and non-exposed persons was found to be less than 1.6 in all tested cancers of A-bomb survivors. They had all been exposed to radiation doses in the order of of 1 Sv (Thompson *et al.* 1984). This indicates improved radio-resistance at high radiation doses. The repair induced by a priming dose can be of the “SOS”-type like that found in some procaryotes (Macklis and Beresford 1991, Wolff 1989). Mis-repair would, however, result from the challenge dose or

from a great first dose and not from the priming dose, making it likely that a large radiation dose such as 1 Sv may cause cancer.

It is far from clear that small radiation doses have carcinogenic effects. The guidelines from the International Commission on Radiological Protection (ICRP) are based on the so-called linear, non-threshold (LNT) model stating that cancer incidence increases linearly with dose. The commission argues that this is still the best estimate even at small doses (e.g. low-level radiation – LLR) (Clarke 1996). There are, however, many reports indicating that small doses of radiation may not have carcinogenic effects and even be protective. In some studies on cell cultures, for example, it has been observed that neoplastic transformation is counteracted by a small priming dose, even to a level below the spontaneous rate (Azzam *et al.* 1996).

There are also epidemiological studies indicating that low-dose radiation does not induce cancer, and even give some protection against certain types of cancer (see Fig. 2 and e.g. Cohen 1998 or 1999). This theme has been discussed during many years, and it is difficult to draw any final conclusion (Walinder 1987; Tubiana 1999). It is important that observations on cancer incidence are interpreted in the light of cellular responses.

Both the adaptive effect and the induced radio-resistance involve protection at the cellular level. The adaptive response is due to a stimulation of radiation repair processes, thus protecting cells against the inactivating effect of the «test» dose. Furthermore, cell growth is stimulated by small radiation doses, an effect also seen in various tissues of animals given repeated small dose fractions or protracted low dose rate irradiation. However, in many cases cancer incidence is reduced by small doses. One can argue that there is a contradiction between these various effects, since increased rate of cell production is typically a process that should be expected to enhance and not to counteract development of cancer. Generally, cells that have lethal DNA damage, are no problem with respect to later cancer development. Cells that are able to repair DNA damage have a possibility of erroneous repair and a subsequent activation of oncogenes or inactivation of tumour suppressor genes. (Alberts *et al.* 1994). Thus, on basis of such reasoning one should not expect decreased cancer induction following activation of a process that enable cells to increase cell survival by increased repair.

There are, however, several alternative explanations of how small radiation doses may protect against cancer, although cells are hypersensitive to such doses. Feinendegen (1999) presents, for example, a calculation of the extra, fixed DNA damage resulting from a 10-times increase of background radiation of 1 to 10 mGy per year. He argues that this would mean an extra 10^{-7} to 10^{-6} fixed DNA damage per cell per day, while normal metabolism and reactive oxygen species produce 10^{-1} . Thus, if the extra, continuous radiation in fact induces repair or defence processes protecting individual cells or tissue against DNA damage in general, protection against cancer development will also be a result.

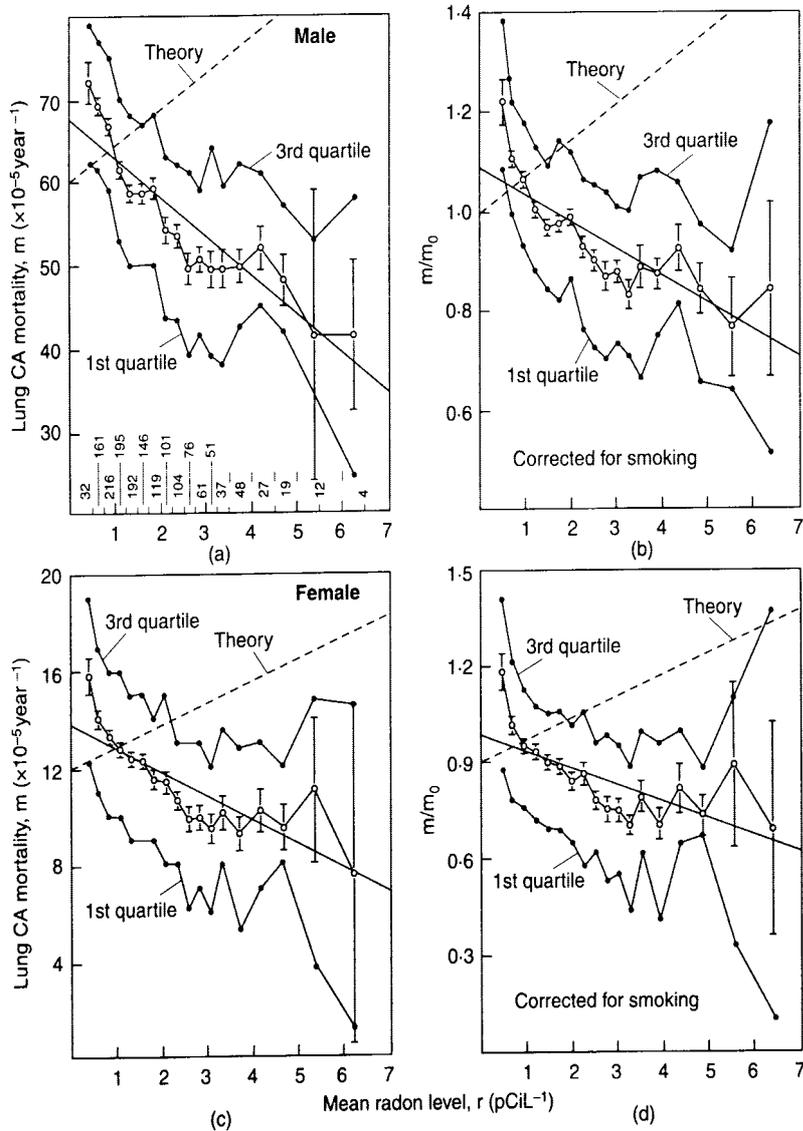


Fig. 2. Age-adjusted lung cancer mortality rates plotted against average radon level in homes of US counties (a) and (c) and corrected for smoking prevalence (b) and (d). Data comprises 1729 US counties and about 90% of the US population. The stipulated line marked “Theory” corresponds to the prediction made from the linear no-threshold theory (LNT), conventionally used for cancer risk estimates. (From Cohen 1999).

On the other hand, small acute single doses of X- or γ -rays will produce damages in a very short time. Many of these will be double-strand breaks of the DNA. Under normal conditions cells have to cope with almost 10^6 damages due to reactive oxygen species produced by normal metabolic activity (Feinendegen 1999). The DNA double strand breaks induced by the acute, low radiation dose may be sufficient to activate induced resistance, which may protect cells even against damage due to metabolism and thereby against cancer development.

Alternatively, there may, however, be a protection against cancer by low-level radiation even without any repair of DNA damage following such doses. The low-dose hypersensitivity means that damaged cells tend to lose their clonogenic potential. The very steep cell survival curve at such low doses (an initial α -value 50-700 times larger than the α -component of the remainder of the irradiated population (Wouters and Skarsgard 1998)) imply that cell death is the preferred endpoint for damaged cells in the initial dose range. There have been various speculations regarding the nature of this cell death. However, with respect to protection against cancer development the nature, or the mechanism, of the radiation-induced cell death does not necessarily be of any importance?. The crucial point is probably that a few cells are losing their clonogenic potential due to the low-dose radiation. Since cells of normal and cancer origin may have the same hypersensitivity (Raaphorst and Boyden 1999; Alsbeith *et al.* 1999), this probably affects normal, unharmed cells as well as cells having a mutation or a misrepaired DNA damage of some kind, which could represent a potential for later cancer development. If cells killed by low-dose radiation are replaced by cells having a relatively intact DNA and therefore a smaller potential for cancer development, the cell killing and replacement process may inevitably represent a small protection against cancer. The benefit thus depends on two cellular consequences of the small dose: The few unharmed cells that are killed and replaced, are of no danger to the organism. On the other hand the few cells with DNA damage caused by metabolic or other processes that were killed by the low-dose radiation and replaced with unharmed cells, would mean that the over-all potential for later cancer development in the organism as a whole would be reduced. Thus, low dose radiation may have a washing-effect on the tissues with respect to cancer development, i.e. it washes away loci of potential danger for cancer development. The effect of low-dose radiation on highly differentiated cells without possibility of proliferation or replacement by stem cells is of little consequence for the organism, since such cells maintain their function even after relatively high doses of radiation.

This seems to turn the logic in Clarke's argument (1996) upside-down: "*First and foremost, there is unlikely to be a threshold in the dose-response curve. DNA repair of double strand breaks is not error free.*" By inducing sudden cell kill instead of repair in some cells having previously misrepaired DNA, and having these cells replaced with newly produced, unharmed cells, low-level radiation may result in an over-all protection against cancer.

At larger radiation doses the situation is different. For cells of repopulating tissues, the initial steepness of the survival curve as analysed by the two-component model, is often in the range $\alpha_s \approx 10$ or higher (Lambin *et al.* 1996; Short *et al.* 1999). If the survival curve had followed this steep slope up to a dose of for example 0.5 Gy, cell survival would be less than 1%. Thus, if cells at the dose level of 0.5 Gy, maintained the same radiosensitivity as for very low doses, even 0.5 Gy would be sufficient to destroy the function of many tissues. When

given to the body as a whole, this would most certainly be lethal. The logic consequence is that cells activate regulatory processes at this dose level, which increase cell survival enormously, even though this increases the danger of later cancer development. In order to avoid sudden damage or death it is better for the organism as a whole to take the chance of a later disease. While tissues can well tolerate a sudden loss of a few cells, they cannot afford sudden loss of a major fraction of the cells.

Thus, the effect of small and large doses of radiation may be dualistic: In regenerating tissues small doses may induce a sudden loss of a few cells, which have to be replaced from the pool of stem cells, but may protect against cancer in the long run. Large doses result in repair (and misrepair) and stimulated cell proliferation, which is life-saving in the short run, but slightly carcinogenic in the long run. Different tissues of the same body may respond differently to radiation at both dose levels.

In conclusion, various hypotheses try to explain reports of serious deviations from the conventional risk calculations following low-level radiation. They all have to be tested mechanistically in each step before a final evaluation. The reports on such deviations should be taken seriously, since they may be more easily explained from a cellular point of view, than predicted from the conventional LNT theory.

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Radon: a likely carcinogen at all exposures

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Abstract

Radon is a well-established lung carcinogen that has been extensively studied. Very high concentrations can occur in some underground mines. Concentrations also tend to build up in homes. Epidemiological studies of radon-exposed miners and of residential radon and lung cancer are reviewed. Quantitative estimates of the risk of lung cancer, based on the experience of the miners, are applied to residential radon exposures in the United Kingdom. Strategies for the prevention of lung cancer induced by residential radon are discussed. Estimates are uncertain, but residential radon is probably responsible for about 2000 lung cancer deaths per year in the United Kingdom, or around 6% of the total, making it the second biggest cause after smoking. Over 80% of the deaths are estimated to occur at ages less than 75 and over 80% in smokers or ex-smokers. Around 90% of radon-induced deaths in the United Kingdom probably occur as a result of exposures to radon concentrations below the currently recommended action level of 200 Bq m⁻³. Further work is needed to obtain more reliable estimates of the risk of lung cancer associated with residential radon and on the cost-effectiveness of various intervention strategies before the most appropriate policies can be developed for managing exposure to this natural carcinogen.

Introduction

Radon-222 is a chemically inert radioactive gas with a half-life of 3.8 days, giving rise to a series of short-lived progeny (Fig. 1). It arises from the decay chain of uranium-238, which is present throughout the earth's crust, and seeps out of rocks, soil and water. If radon itself is inhaled, some will be absorbed through the lung, but the majority will be exhaled. However, the progeny are solid and form into small molecular clusters or attach to aerosols in the air and these may be deposited on the bronchial epithelium. Two of the short-lived progeny in

in the concentrations commonly observed. In the great majority of countries radon is the principal source of exposure of the general population to ionizing radiation [2], and substantial efforts are being directed towards estimating its effect in the general population. Residential radon concentrations can usually be reduced through relatively simple measures, and several countries now have recommended control strategies.

The BEIR VI Committee published a comprehensive report on the health effects of radon in 1999 [1]. Its effects have been reviewed twice by the International Agency for Research on Cancer [3,4], which led to its classification as a human carcinogen (group 1), and other reviews have also been published recently [5]. The present article draws on these reports and summarizes the quantitative evidence relating to lung cancer in radon-exposed miners and recent work studying directly the risk of residential radon. It also describes the implications of the risks seen in radon-exposed miners for the general population of the UK and describes current strategies for the prevention of radon-induced lung cancer.

Lung cancer in radon-exposed miners

It was appreciated as early as the 1500s that metal miners in the Erz mountains in central Europe had a very high mortality rate from respiratory disease. However, it was not until early in the 20th century that the disease was established as being lung cancer and not until the 1920s, when high levels of radon were identified in these mines, that radon was first postulated as the cause. Support for this postulate was by no means universal, however, and alternative causal theories were also popular, including the effects of dust exposure and metals in the ore, and an increased susceptibility resulting from inbreeding in the small mining communities. It was only in the 1950s and 1960s, when studies of igneous rock miners in other areas, who were also exposed to high radon levels, also revealed unusually high lung cancer rates, that radon was generally accepted as the cause. Since that time, ventilation and other measures have been used to reduce radon levels in most affected mines that continue to operate. This has reduced the risk of occupationally-induced cancer from radon, although it still remains an issue both for those who are currently employed in affected mines and for those who have been employed in the past.

Studies have been carried out of the mortality patterns of several groups of radon-exposed miners and these form the major body of available evidence concerning the consequences of exposure to radon and its decay products. At present, results have been published of eleven major studies, covering a total of over 60,000 miners in Europe, north America, Asia and Australia, among whom over 2,500 deaths from lung cancer have occurred. These studies all include quantitative information on the radon exposures received by the men and many of them also include information on unexposed workers, e.g. surface workers, as an internal comparison group. Eight of the studies are of uranium miners; the remainder are of miners of tin, fluorspar or iron. In contrast to the findings for lung cancer, there is little evidence of any association between radon exposure and mortality from other cancers [6] or other diseases [1] in the same miners.

Table 1. Lung cancer mortality in cohort studies of underground miners occupationally exposed to radon

Study and reference	Type of mine	Number of exposed miners	Mean total WLM	Mean duration of exposure (years)	Number of lung cancer deaths	Percentage increase in age-specific risk of lung cancer perWLM ^a	95%confid. interv.
Yunnan, China [7]	Tin	13,649	286.0	12.9	936	0.16	0.1-0.2
W. Bohemia, Czech Republic [8]	Uranium	4,320	196.8	6.7	701	0.34	0.2-0.6
Colorado, USA ^b [9]	Uranium	3,347	578.6	3.9	334	0.42	0.3-0.7
Ontario, Canada ^c [10]	Uranium	21,346	31.0	3.0	285	0.89	0.5-1.5
Newfoundland, Canada [11]	Fluorspar	1,751	388.4	4.8	112	0.76	0.4-1.3
Malmberget, Sweden [12]	Iron	1,294	80.6	18.2	79	0.95	0.1-4.1
New Mexico, USA [13]	Uranium	3,457	110.9	5.6	68	1.72	0.6-6.7
Beaverlodge, Canada [14]	Uranium	6,895	21.2	1.7	56	2.21	0.9-5.6
France [15]	Uranium	1,769	59.4	7.2	45	0.36	0.0-1.2
Port Radium, Canada [16]	Uranium	1,420	243.0	1.2	39	0.19	0.1-0.6
Radium Hill, Australia [17]	Uranium	1,457	7.6	1.1	31	5.06	1.0-12.2
Total ^d		60,606	164.4	5.7	2,674		

a The working level (WL) is defined as any combination of the short-lived radon progeny in one litre of air that results in the ultimate release of 1.3×10^5 MeV of potential α -particle energy. Exposure to this concentration for 170 h (or twice this concentration for half as long, etc.) is defined as a working level month (WLM). An individual living in a house with a radon concentration of 20 Bq m^{-3} will be exposed to 0.08 WLM per year.

b Totals given exclude data above 3200 WLM. c Values given include all uranium miners, including those with previous gold mining experience.

d Totals adjusted for miners and lung cancers included in both Colorado and New Mexico studies.

Source: BEIR VI Committee [1]

In each of the eleven studies, there was a close correlation between radon exposure and lung cancer risk, with miners who had higher exposures experiencing a greater increase in risk than those who had lower exposures, and in every study the relationship was so strong that it was unlikely to be due to chance (Table 1). Although the size of the radon-related increase varied by more than an order of magnitude between the different studies, analysis of the information in the individual studies revealed some clear systematic trends in risk. The relative risk of lung cancer (i.e. the proportionate increase in the age-specific risk of lung cancer) rose linearly with increasing cumulative exposure, both overall and in the region <600 WLM, which is of greatest interest when considering the effects of residential exposures (Fig. 2).

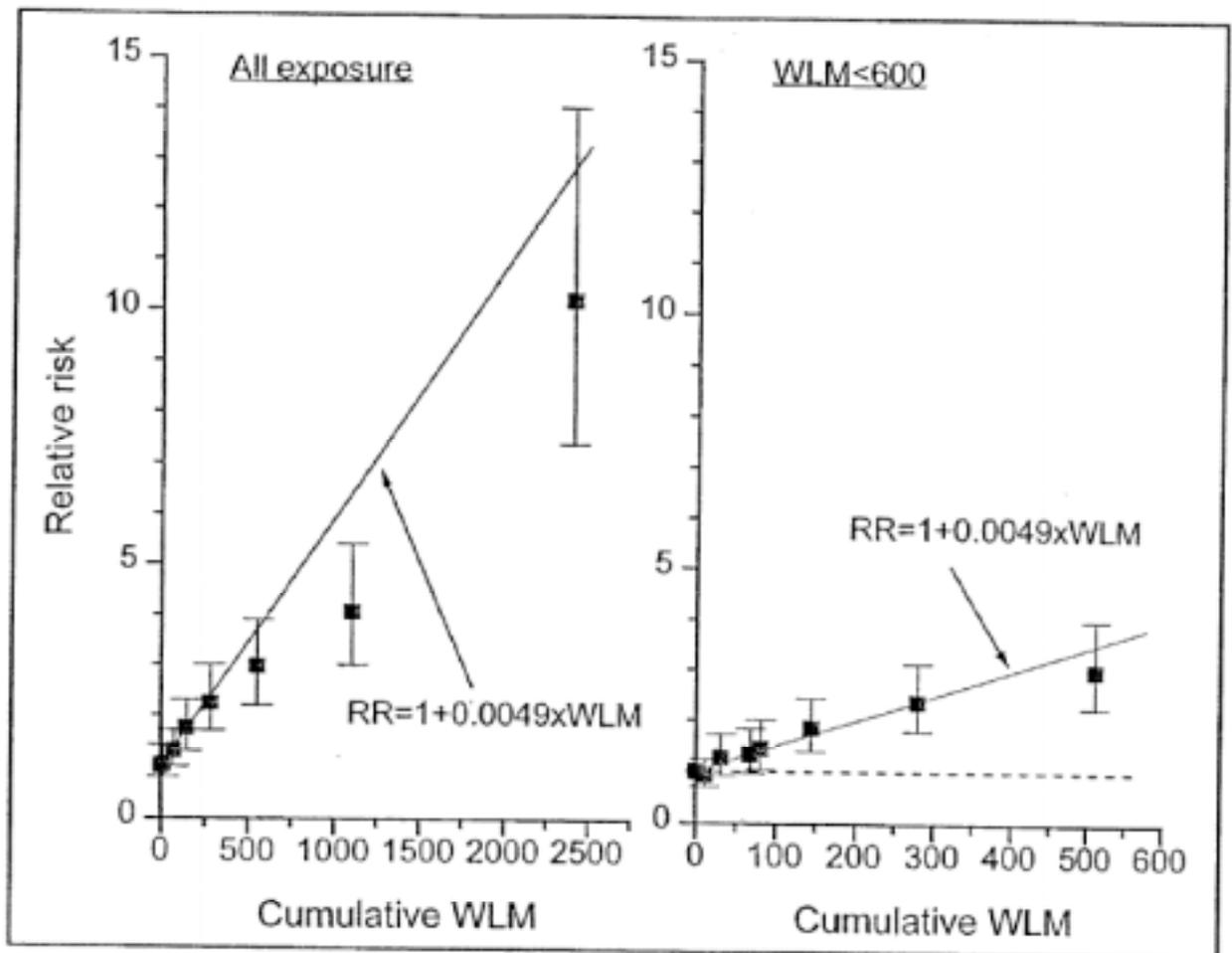


Fig. 2. Relative risk (RR) of lung cancer with cumulative radon exposure in the cohort studies of underground miners occupationally exposed to radon (based on [18]).

After allowing for a minimum latent period of around five years between exposure and death, the percentage increase in risk was higher in the period around 10 years after exposure, than at 20 or 30 years after exposure. In addition, the percentage increase in lung cancer risk was also greater in individuals who were aged around 50 than in individuals who were aged around 60 or 70. Finally, mines where the radon concentrations were relatively low, had a larger percentage increase in risk per unit exposure than mines with higher radon concentrations or, equivalently, a given total exposure was associated with a greater increase in risk if it was received over a longer rather than a shorter time period.

In view of the variations in the risk per unit exposure with time since exposure, age, and radon concentration, it is difficult to combine the results of the different studies appropriately using just the information published by the individual studies. To overcome this difficulty, the individual data from the eleven studies were collated centrally, and a combined analysis carried out by the BEIR VI Committee [1]. After extensive technical investigations the preferred form of the model relating radon exposure to risk of death from lung cancer was:

$$R=100\beta w^* \varphi_{\text{age}} \gamma_z, \quad (1)$$

where R is the percentage increase in the risk of death from lung cancer for a person of a certain age with a given history of exposure to radon; β is the parameter relating lung cancer risk to history of radon exposure; w^* represents the radon exposure and takes the form of a weighted average,

$$w^* = (w_{5-14} + \theta_{15-24} w_{15-24} + \theta_{25+} w_{25+}) \quad (2)$$

with w_{5-14} , w_{15-24} , and w_{25+} representing the exposure incurred during the periods 5-14, 15-24, and 25+ years prior to the current age. The coefficient of w_{5-14} is equal to one, while θ_{15-24} and θ_{25+} represent the contributions to risk from exposures received 15-24 years and 25+ years previously, compared to exposures received in the period 5-14 years previously. The parameter φ_{age} represents the modifying effect of age, while the parameter γ_z represents the modifying effect of either radon concentration or of exposure duration. Estimates of the parameters β , θ_{15-24} , θ_{25+} , φ_{age} , and γ_z for both the exposure-age-duration and the exposure-age-concentration formulation of the model are given in Table 2.

In most of the miner populations that have been studied, the majority of the men would have been cigarette smokers and, in most cases, this will have had an effect on their lung cancer risk that is even greater than that from their radon exposure. The effect of radon exposure can be expected to differ between smokers and non-smokers, depending on the way in which the risks of smoking and radon exposure act jointly. Unfortunately, no smoking information is available for five of the miners' studies. Among the six studies for which some smoking information is available, 2798 lifelong non-smokers could be identified, who between them had experienced 64 lung cancers.

Table 2. Parameter estimates from BEIR VI [1] preferred models in combined analysis of eleven studies of underground miners occupationally exposed to radon. See text for description of models

Exposure-age-duration model ^a		Exposure-age-concentration model	
$\beta \times 100^{b,c}$	0.55 ^d	$\beta \times 100^{b,c}$	7.68 ^d
Time-since-exposure windows		Time since-exposure windows	
θ_{5-14}	1.00	θ_{5-14}	1.00
θ_{15-24}	0.72	θ_{15-24}	0.78
θ_{25+}	0.44	θ_{25+}	0.51
Attained age (years)		Attained age (years)	
$\phi_{<55}$	1.00	$\phi_{<55}$	1.00
ϕ_{55-64}	0.52	ϕ_{55-64}	0.57
ϕ_{65-74}	0.28	ϕ_{65-74}	0.29
ϕ_{75+}	0.13	ϕ_{75+}	0.09
Duration of exposure (years)		Concentration of exposure (WL ^e)	
$\gamma_{<5}$	1.00	$\gamma_{<0.5}$	1.00
γ_{5-14}	2.78	$\gamma_{0.5-1.0}$	0.49
γ_{15-24}	4.42	$\gamma_{1.0-3.0}$	0.37
γ_{25-34}	6.62	$\gamma_{3.0-5.0}$	0.32
γ_{35+}	10.2	$\gamma_{5.0-15.0}$	0.17
		$\gamma_{15.0+}$	0.11

a Risk projections for the US were carried out by the BEIR VI Committee for both models and shown to give very similar results. In the present paper projections based on the exposure-age-concentration model are given. B Units are WLM⁻¹. c See Table 1 for definition of WLM and WL. d When separate estimates are required for smokers and non-smokers these are 0.50 for ever-smokers and 1.1 for never smokers in the exposure-age-duration model, and 6.90 for ever smokers and 15.3 for never-smokers in the exposure-age-concentration model.

This was not enough to carry out a full analysis, but the relationship between the relative risk of lung cancer and cumulative radon exposure could be compared in lifelong non-smokers and others. In both groups the relationship between the relative risk of lung cancer and cumulative radon exposure was approximately linear, but the *relative risk* per unit exposure was considerably greater among the lifelong non-smokers than among the current and ex-smokers (Fig. 3). To allow for this, a higher value of β was recommended in equation (1) above for non-smokers and a slightly lower value for smokers, when separate estimates were

required for lifelong non-smokers and current or previous smokers (see Table 2 for parameter values).

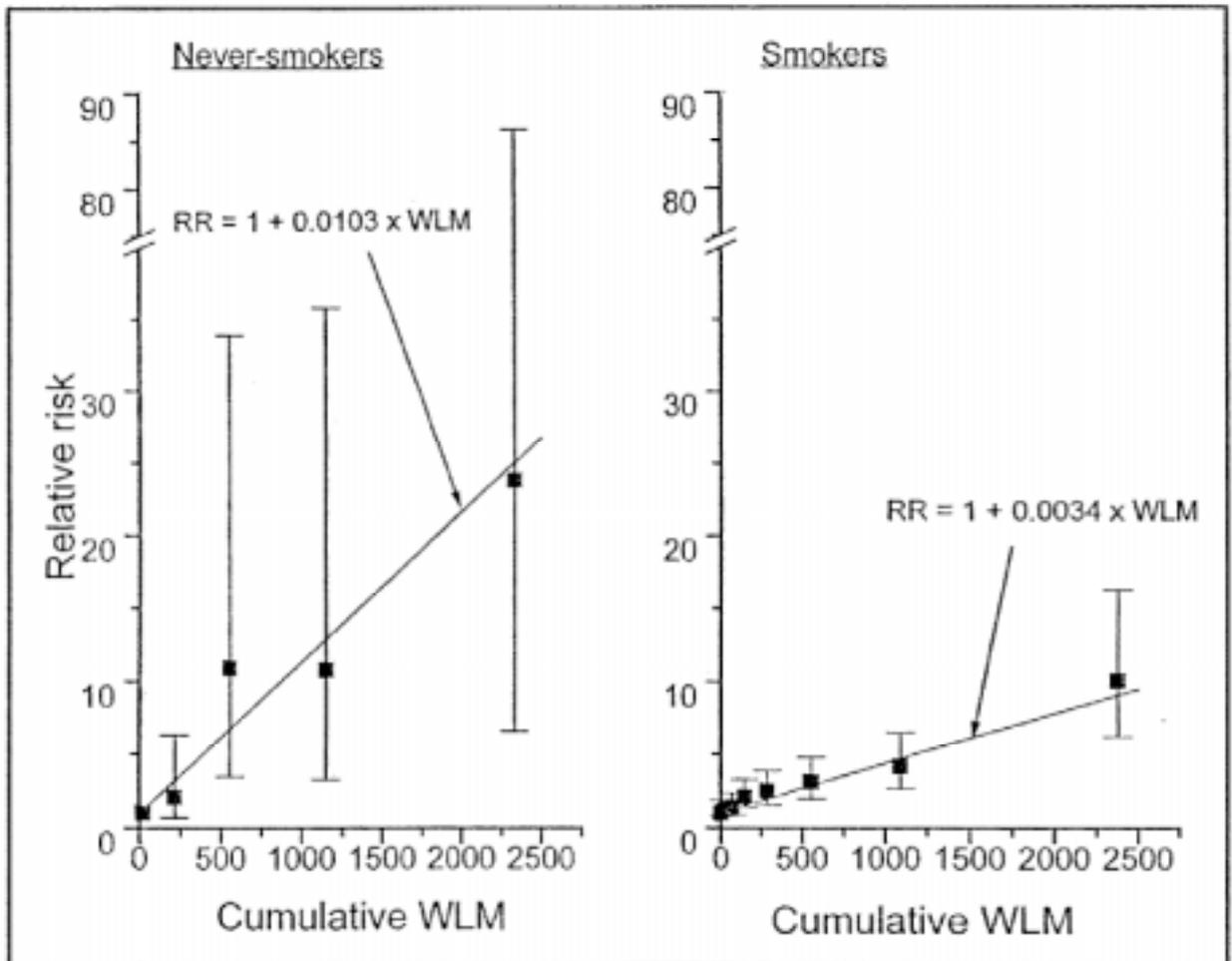


Fig. 3. Relative risk (RR) of lung cancer with cumulative radon exposure among lifelong non-smokers and others in the six cohort studies of underground miners for which smoking information was available (based on [18]). Although the increase in *relative risk* per unit exposure is higher for never smokers than for smokers, the increase in *absolute risk* will be higher for smokers, as they have much higher rates of lung cancer.

Lung cancer from residential radon

Average exposures received by the miners are an order of magnitude or so greater than average indoor exposures and their average duration of exposure was less than six years (Table 1). The miners were almost all adult males, the information about both their radon exposure and their smoking habits is crude and subject to error, and their conditions of exposure differ substantially from those in homes, with the miners carrying out substantial amounts of heavy work in an atmosphere polluted by dust and fumes. There is, therefore, great uncertainty in applying risk estimates derived from studies in miners to the effects of residential radon, and direct estimates of the risks of residential radon are needed. At the present time, 14 major studies of residential radon have been published (Table 3). These are case-control studies, in which detailed residential and smoking histories have been gathered for a series of individuals with lung cancer and a series of control subjects, who had not developed the disease. The radon concentration has then been measured over a period of several months in the air of the subject's present and previous homes using passive alpha track detectors and the weighted average radon concentration during an appropriate time period has been calculated. To date, most of the studies have had inadequate power to detect a risk on their own, although a weighted average of the published results is indicative of a risk (estimated relative risk at 100 Bq m^{-3} compared with 0 Bq m^{-3} 1.06, 95% confidence interval 1.01-1.10, see Table 3).

Most of the estimates shown in the main body of Table 3 have been obtained using standard statistical methodology for case-control studies in which it is assumed that the average radon concentration to which an individual has been exposed, can be assessed without error. However, this assumption is usually violated in two different ways.

Firstly, in most of the studies there are some time-periods for which it is not possible to obtain a radon measurement, for example, because the home previously occupied by the subject had been demolished. Radon concentrations for such missing periods need to be estimated in the analysis.

Secondly, even where it has been possible to obtain a measurement, the measured value will be subject to uncertainty in the sense that repeated measurements in the same home vary with a coefficient of variation of around 50% [23,28].

These two different sources of uncertainty will have different effects on the results of an analysis that has been carried out using standard techniques [34]. Missing values that have been replaced by estimates will cause confidence intervals to be wider than they would otherwise have been, and are undoubtedly a contributing factor in the low power of the case-control studies in shown in Table 3. In contrast, the presence of uncertainty in measured residential radon concentrations will cause the estimated effect of the radon using standard techniques of analysis to be biased towards zero. For two of the case-control studies shown in Table 3, analyses have been carried out that take this bias into account [23,28]. For these studies, the estimated relative risks of lung cancer at 100 Bq m^{-3} compared with 0 Bq m^{-3} using the standard methods were 1.10 (95% confidence interval 1.01, 1.22) and 1.08 (0.97,

1.20), while the estimates taking account of measurement uncertainty were somewhat higher, at 1.17 (1.03, 1.37) and 1.12 (0.95, 1.33).

Rather than measuring the current concentration of radon in the air of all the homes of interest, an alternative method of assessing residential radon histories is to estimate an individual's cumulative radon exposure. This can be done by estimating the accumulation of the long-lived radon decay product Pb-210 implanted in the glass surface of an object, such as a picture frame, that has been on display in all the subject's homes for a substantial period of time. The long-lived Pb-210 in turn gives risk to a shorter lived product, Po-210, which can be measured using passive alpha track detectors. From this measurement an estimate can be made of the cumulative radon exposure in the rooms where the glass object has been kept. The uncertainties associated with this method of estimating radon histories have not yet been fully documented, but it should avoid the difficulties caused by missing measurements in subjects' previous home and also the problem that in some countries residential radon concentrations may have changed systematically over time, for example because of a tendency to reduce indoor ventilation rates [35], which would mean that air concentrations measured at the present time would be systematically biased compared with previous values. At the present time only one study has published a risk estimate based on cumulative exposure histories from surface monitors [29]: this gave an estimated relative risk at 100 Bq m⁻³ compared with 0 Bq m⁻³ of 1.63 (95% confidence interval 1.07, 2.93), while the same study failed to show any positive relation using conventional air monitors, with estimated relative risk at 100 Bq m⁻³ compared with 0 Bq m⁻³ 0.85 (0.73, 1.00).

Despite the uncertainties that affect the results of the case-control studies of residential radon, the risks suggested by them are in good agreement with the estimated risks based on the studies of miners (Figure 4). However, public perception of residential radon has been confused, especially in the United States, by the wide publicity given to an ecological study in which average residential radon concentrations in several hundred US counties have been correlated with the county-specific lung cancer incidence rates after adjusting at the county level for various other factors that might affect lung cancer risk including smoking habits [37]. The results of the ecologic study show a negative association at the county level between residential radon exposure and lung cancer risk, and are clearly out of line with the results of both the miners studies and the case-control studies of residential radon. There is ample evidence to suggest that the results of the ecological study are incorrect, and it can be shown theoretically that adjusting for smoking at the county level will not remove the effect of this factor, which is responsible for the majority of cases of lung cancer [38]. For further discussion of this topic, see [1,4,39,40].

Table 3. Estimates of relative risk (RR) at 100 Bq m⁻³ compared with 0 Bq m⁻³ and 95% confidence intervals (CI) in epidemiological studies of residential radon and lung cancer based on at least 100 cases of lung cancer and direct measurements of radon using α -track monitors^a

Study and reference	Cases of lung cancer	Control subjects	RR	95% CI
New Jersey, USA [19]	480	442	1.49	(0.89-1.89)
Shenyang, China [20]	308	356	0.95	(undefined-1.08)
Stockholm, Sweden [21]	201	378	1.16	(0.89-1.92)
Swedish nationwide [22,23]	1281	2576	1.10	(1.01-1.22)
			1.17 ^b	(1.03-1.37)
Winnipeg, Canada [24]	738	738	0.98	(0.87-1.27)
Missouri, USA I [25]	538	1183	1.08	(0.95-1.24)
South Finland [26]	164	331	1.80	(0.90-3.50)
Finnish nationwide [27]	517	517	1.11	(0.94-1.31)
South-West England [28]	982	3185	1.08	(0.97-1.20)
			1.12 ^c	(0.95-1.33)
Missouri, USA II [29]	247 ^d	299 ^d	0.85 ^d	(0.73-1.00) ^d
	372 ^e	471 ^e	1.63 ^e	(1.07-2.93) ^e
Iowa, USA [30]	413	614	1.24	(0.95-1.92)
Western Germany [31]	1449	2297	0.97 ^f	(0.82-1.14)
			1.09 ^g	(0.86-1.38)
Eastern Germany [32]	1053	1667	1.11 ^f	(1.00-1.27)
			1.27 ^g	(1.00-1.60)
Swedish never-smokers [33]	258	487	1.28	(0.95-2.05)
Total ^h			1.06	(1.01-1.10)

^a Based on [4] with additions. ^b Assuming 50% coefficient of variation in measured radon concentration. ^c Assuming 50% coefficient of variation in measured radon concentrations and allowing for uncertainties in estimates of missing values. ^d Analysis based on air monitors. ^e Analysis based on surface monitors. ^f Entire study. ^g High radon areas

^h Total is weighted average of all studies. Where two estimates are given for a study the first entry has been used.

Table 4: Causes attributed to the lung cancer deaths occurring each year in the United Kingdom

Cause	Lung cancer deaths	Percentage attributed	
Not caused by active smoking or by residential radon	3,351	9.6	
Caused by radon but not by smoking	349	1.0	} 6.5 due to residential radon
Caused by smoking and radon (avoidance of either of which would have avoided that particular lung cancer)	1,926	5.5	
Caused by smoking and not by radon	29,332	83.9	} 89.4 due to active smoking
Total no. of lung cancer deaths	34,958	100.0	

Calculation based on 1998 UK national data for numbers of lung cancer deaths, population size and smoking habits [42,43]. Lung cancer death rate in lifelong non-smokers taken from a US prospective study of mortality [44], adjusted for the lower average radon level in the UK. Average radon exposure assumed to be 20 Bq m⁻³ [45]. BEIR VI exposure/age/concentration model with submultiplicative joint effect of smoking and radon assumed for radon risks. Additional assumptions are those used in the BEIR VI Committee's projections [1].

Implications for the UK of risks seen in radon-exposed miners

Despite the uncertainties in extrapolating from the experience of radon-exposed miners to the effects of residential radon, the most appropriate approach at present to estimating the likely numbers of deaths caused by radon, both by itself and in conjunction with smoking, is from the BEIR VI Committee's preferred model. In order to understand the implications of the BEIR VI model for the United Kingdom, it has been combined with UK data on smoking habits, population size, numbers of deaths from lung cancer for males and females in different age groups, and lung cancer rates among lifelong non-smokers. As survival after a diagnosis of lung cancer is very poor [41], projections for lung cancer incidence would be very similar to those given here for mortality.

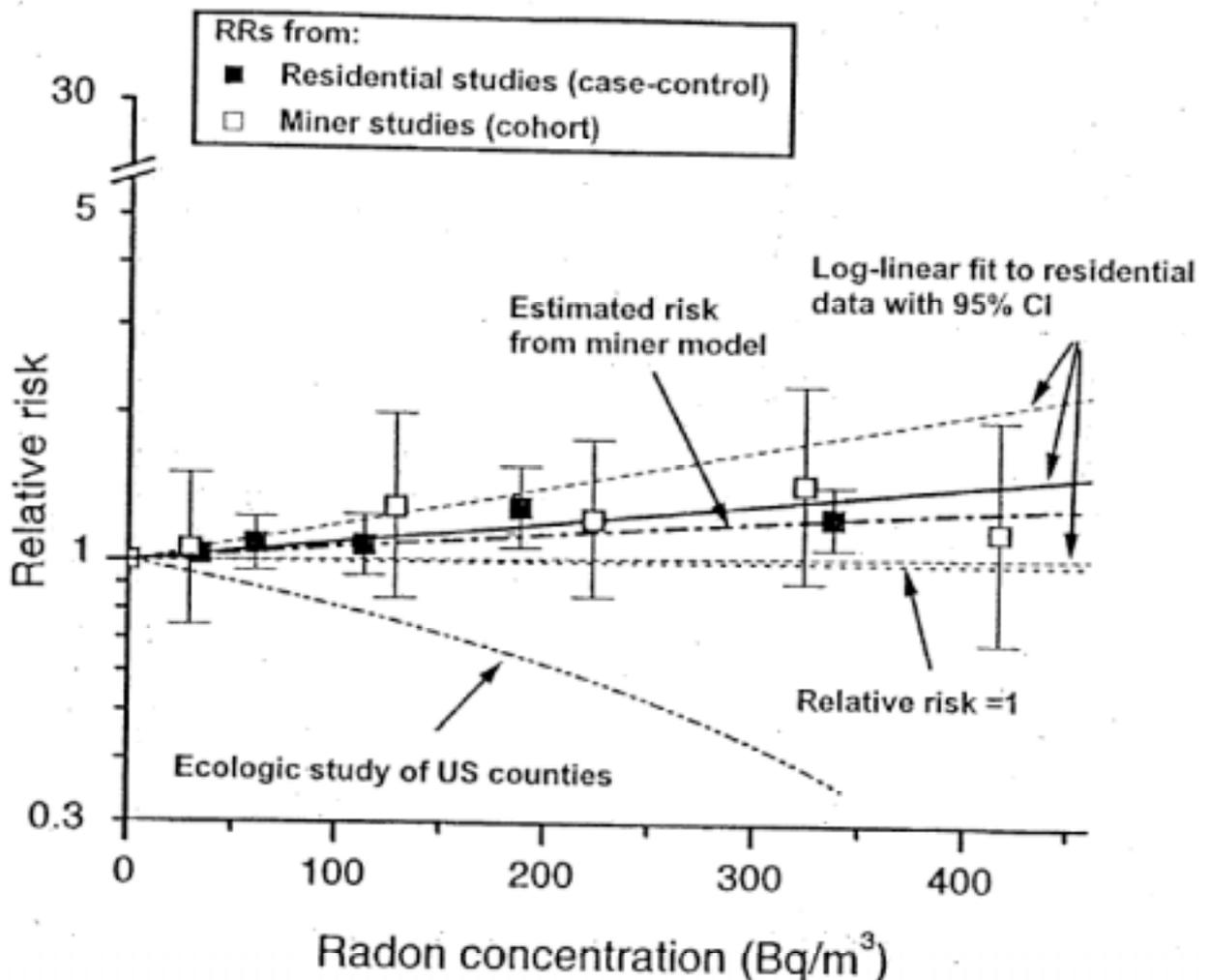


Fig. 4. Summary relative risks (RR) from meta-analysis of published data from case-control studies of residential radon [36], pooled analysis of cohort studies of miners occupationally exposed to radon [18], and an ecologic study of 1601 US counties [37]: the negative slope in the ecologic study is approximately 10 times its standard error (figure based on [1]).

These calculations suggest that of the 34,958 lung cancer deaths that occurred in the UK during 1998, 2275, or 6.5% of the total, were caused by radon (Table 4). Of these, only 349 (1.0% of all lung cancer deaths) can be attributed to radon acting alone, while the remaining 1926 (5.5% of all lung cancer deaths) were caused by both radon and smoking in the sense that the lung cancer could have been avoided by avoiding either smoking or radon exposure. Lung cancer in the UK is primarily attributable to smoking and lung cancer rates are higher in

males than in females; as a result, 62% of the deaths attributable to radon are projected to have occurred in males, with only 38% in females (Table 5). It is likely that two thirds of the deaths occurred in individuals between the ages of 55 and 75, with the remainder approximately equally divided between individuals aged 35-54 and 75+. Very few radon-attributable deaths are likely to occur in individuals under the age of 35.

Personal risks will not be uniformly distributed throughout the population and will be determined by both smoking status and residential radon concentration. The likely extent of this variation can be seen when lung cancer mortality rates for individuals with different smoking habits and residential radon concentrations are considered in conjunction with the BEIR VI risk models. The best estimate of lung cancer mortality rates in lifelong non-smokers are those obtained from the American Cancer Society's prospective study [44]. These have been adjusted, according to the BEIR VI model, to take into account the lower average residential radon concentrations of 20 Bq m⁻³ in the UK [45] compared with 46 Bq m⁻³ in the US [2]. At 20 Bq m⁻³ the cumulative risk to age 85 of death from lung cancer in non-smokers is estimated to be 0.8% (Table 6). This would be reduced only very slightly, to 0.7%, if the residential radon concentration were, hypothetically, brought down to zero, and would rise to 1.4% at 200 Bq m⁻³, the level at which it is recommended in the UK that action be taken to reduce radon levels, and further to 2.2% at 400 Bq m⁻³.

Table 5: Lung cancer deaths attributable to residential radon in the United Kingdom each year by age and sex

Age	Males	Females	Total
<35	1.5	1.5	3 (<1%)
35-54	224	161	385 (17%)
55-74	962	554	1516 (67%)
75+	218	153	371 (16%)
All ages	1405 (62%)	869 (38%)	2275 (100%)

For continuing cigarette smokers, estimates of the age-specific lung cancer death rate are available from a recent study of smoking and lung cancer in the UK [46]. These suggest that the cumulative risk of death from lung cancer by age 85 is around 30% for individuals whose residential radon concentrations are equal to the UK average, but rises substantially, to around 40% for those exposed at 200 Bq m⁻³ and to 49% for those exposed at 400 Bq m⁻³. For the entire population, which consists of a mixture of lifelong non-smokers, current smokers and ex-smokers, the estimates lie in between those for lifelong non-smokers and current cigarette

smokers (Table 6). Estimates are lower for females than for males, reflecting the fact that in the UK women have smoked less in the past than men, so that current lung cancer rates for the country as a whole are lower in women than in men.

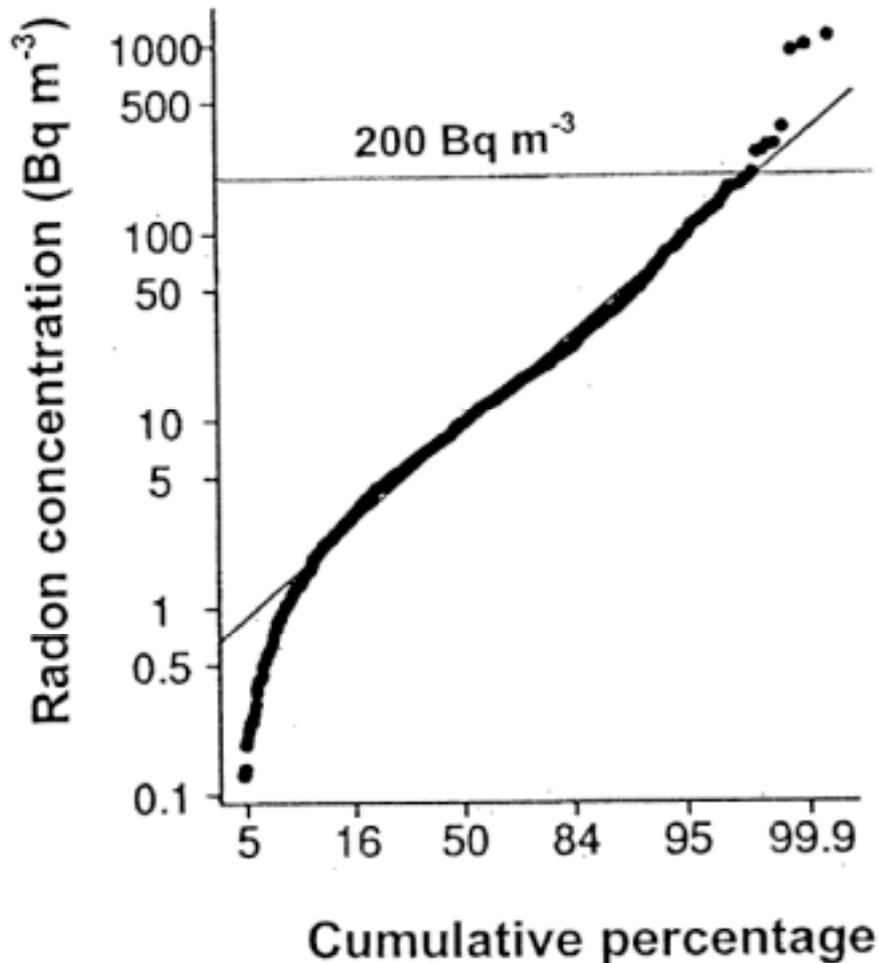


Fig. 5. Log-normal probability plot of residential radon concentrations from the UK national survey [45], adjusted for the outside air concentration (i.e. concentrations less than or equal to 4.1 Bq m^{-3} are set to 4.1 Bq m^{-3} , and 4 Bq m^{-3} is then subtracted from all concentrations. Solid line indicates best fitting straight line. Figure based on [47].

The number of deaths attributable to radon at each level of concentration is determined by not only these individual risks, but also by the distribution of residential radon concentrations throughout the country. For the UK, residential radon levels have been shown to follow a log-normal distribution after allowance for the radon level in outside air, which is around 4 Bq m^{-3} and varies relatively little (Fig. 5). These data suggest that less than 1% of homes in the UK have a radon concentration of above 200 Bq m^{-3} . Consequently, the proportion of the lung

cancer deaths attributable to radon that occur as a result of exposure to residential radon concentrations of 200 Bq m⁻³ or more, is only around 10%, with another 13% occurring at concentrations in the range 100-199 Bq m⁻³ (Table 7). In contrast, over one third of radon-attributable deaths are estimated to occur with radon concentrations of less than 25 Bq m⁻³, and around 20% each at levels in the ranges of 25-49 Bq m⁻³ and 50-99 Bq m⁻³.

Table 6. Effect of various residential radon concentrations on the cumulative risk (%) of death from lung cancer to age 85

	Residential radon concentration (Bq m ⁻³)				
	0	20 ^a	100	200	400
Lifelong non-smoker	0.7	0.8	1.0	1.4	2.2
Cigarette smoker	29.1	30.4	34.8	40.0	49.3
Whole population:					
Males	9.8	10.4	12.4	14.8	19.6
Females	4.4	4.7	5.7	7.0	9.5

Based on the BEIR VI exposure/age/concentration model for radon risks with submultiplicative joint effect of smoking and radon (lifelong non-smokers and cigarette smokers) or no adjustment for smoking (whole population) [1]. Lung cancer death rates based on 1988 UK national data [42] for whole population, a US prospective study [44] for lifelong non-smokers (with adjustment for the lower average radon concentration in the UK compared with the US), and a recent study of UK lung cancers for cigarette smokers [46]. If, for one particular category, the lung cancer rates per 105 in all the five year age groups before age 85 add up to c , then the cumulative risk by age 85 is $1 - \exp(-5c/10^5)$. Thus, cumulative risks depend only on age-specific lung cancer rates and not on competing causes of death.

^aUK average residential radon concentration.

Prevention of lung cancer from residential radon

A recent international survey of radon legislation and national guidelines [48] has shown that most European and many non-European countries now have recommended procedures for controlling levels of indoor radon. Some countries also have guidelines against radon incorporated into their building codes and recommended construction techniques. In most cases the guidelines are formulated in terms of action levels for dwellings and workplaces,

above which it is advised that remedial measures be taken. These action levels vary between countries, from 150 to 1000 Bq m⁻³.

The identification of existing homes with radon concentrations above such action levels is the necessary first step towards reducing the risks that individuals living in them for long periods are likely to experience (Table 6). With this in mind the UK government has offered free radon measurements for all homes in areas in England estimated to have more than a 5% chance of having a radon level above the UK action level for dwellings of 200 Bq m⁻³. Up to a third of those approached took advantage of this policy, and around 400,000 measurements were carried out as a result [49].

However, only around 10-20% of those living in homes that were identified to be above 200 Bq m⁻³ took any radon remedial action [50,51]. Current UK government efforts have therefore been directed towards supporting local authority led initiatives that will increase this percentage, such as additional publicity materials and training for local authority staff and local builders. Pilot studies have demonstrated that an approximate doubling of the percentage taking radon remedial measures can then be achieved [51].

In considering both the benefits and the costs of radon remediation programmes targeted at homes or other buildings above a specified action level, it is useful to be able to make comparisons with other health related interventions. The methodological framework now considered appropriate in the economic evaluation of health interventions is cost-effectiveness analysis, in which all the direct costs associated with an intervention are divided by the additional health benefits (such as life-years gained) to obtain a cost per unit of health gain, which can then be compared with that for other interventions [52,53]. For radon remediation the data needed for such a model include the per cent of homes over the action level, the cost of identifying these homes, the per cent of these homes where radon remediation is in fact carried out, the cost of radon remediation, the risk of lung cancer per unit radon exposure, the average cost of treatment per lung cancer case, the number of life-years gained per lung cancer case avoided, and also discount rates for ongoing costs associated with radon remediation and for life-years gained.

In the UK, cost-effectiveness studies using this framework have been carried out for interventions to reduce radon concentrations above the action level in both homes and schools for the county of Northamptonshire [54,55]. For homes, a societal cost-effectiveness ratio of £13,250 (\$20,385) per life-year gained was estimated using 1997 prices. The cost of radon remediation is born by the home owner in the UK, and a survey carried out as part of this study found that the average cost of radon remediation in Northamptonshire was £533 (\$820). The figure of £13,250 took the percentage of homes above 200 Bq m⁻³ to be 6.3% and the percentage of such households where remediation work was carried out at 11%, as these were the values observed in Northamptonshire. The cost-effectiveness ratio would, however, decrease if either of these values were to increase. A sensitivity analysis demonstrated that if either the percentage of affected households who actually remediated, increased to 30% or the percent of homes over 200 Bq m⁻³ increased to 15% (as is the case for several areas of the UK [56]), then the cost-effectiveness ratio would decrease to around £5000 (\$7692) per life-year gained. In the UK, interventions to prevent disease that have cost-effectiveness ratios of less than £10,000 (\$15,385) per life year saved, have often been adopted as Government funded

measures (including the national breast cancer screening programme and the secondary prevention of heart disease using statins and many interventions with cost-effectiveness ratios in excess of this range are currently in practice [54]. In the schools study, the cost effectiveness ratio was estimated at £7550 (\$11,615), again at 1997 prices. Once again, this is within the range for health interventions that have often been adopted, although it was found to be less favourable than several of the lung cancer prevention programmes targeted at smoking cessation, which have been shown to have cost-effectiveness ratios per life-year gained of under £1,000 (\$1,539) [55].

If a substantial proportion of the radon attributable deaths are to be avoided, something more will have to be done beyond reducing the levels in homes with concentrations above 200 Bq m⁻³, which account for only 10% of the total (Table 7). The practicability of reducing radon levels in homes with concentrations at much lower radon concentrations consequently needs to be considered. One way in which this might eventually be achieved would be by requiring radon protection measures in all new dwellings. Several countries, including the UK, have recently adopted legislation regarding protective measures in new dwellings [57]. These are aimed specifically at reducing the probability that a new home will have a radon concentration above the current action level of 200 Bq m⁻³ and have therefore been introduced only in ‘radon affected’ areas, where more than 3% of measurements in existing dwellings have been found to be above this level. By requiring protection measures for all new homes, this legislation will clearly have an impact on the entire distribution of residential radon concentrations within these areas, as well as on the proportion above the action level. One study [58], again in Northamptonshire, has concluded that the installation of radon protection measures in all new dwellings in the ‘radon affected’ parts of the county has a cost per unit of radiation exposure avoided, which is similar to that for the current policy aimed at remediating existing dwellings above the action level. However, full economic cost-effectiveness analyses have not yet been published, either of the policies recently introduced in the UK or of a policy of requiring low-cost basic radon protection such as ensuring that the damp-proof barrier is radon-proof and that its edges and any joins in it are appropriately sealed, in all new dwellings.

Conclusion

Radon is an established carcinogen and ubiquitous air pollutant. Evidence from heavily exposed miners and theoretical considerations both suggest that its carcinogenic effects are likely to vary linearly with exposure without any threshold. Quantitative analysis indicates that in the UK, the US [1], and also many other countries, radon is the second most important cause of lung cancer after smoking. It probably causes over a hundred thousand lung cancer deaths worldwide each year, considerably more than the number thought to be caused by passive smoking.

Table 7: Lung cancer deaths attributable to residential radon in the United Kingdom each year by residential radon concentration

Range residential radon concentrations (Bq m ⁻³)	Percentage of homes in range	Deaths attributable to residential radon	
		Number	Percent
0-24	75.3	812	35.7
25-49	14.9	492	21.6
50-99	6.8	445	19.6
100-199	2.3	296	13.0
200+	0.7	230	10.1
Total	100.0	2275	100.0

Radon deserves attention because residential radon levels can usually be reduced, often by relatively simple and cheap intervention measures, raising, at least in principle, the prospect of reducing the number of radon-induced deaths through preventive measures. However, informed discussion on this topic can take place only if precise, unbiased estimates of the risk associated with a given radon concentration are available, together with good information about factors that modify the risk. Several countries have introduced radon-control strategies, yet at present these are often aimed at the small proportion of the population with very high exposures. In contrast, relatively little attention has been directed towards the effects of lower radon concentrations, although the typical log-normal distribution of residential radon concentrations means that this is where the bulk of radon-induced deaths are likely to occur. One reason for this may be that direct evidence of the carcinogenic risk attached to residential radon is at present weak, as the majority of studies of the effects of residential radon have low power. At present efforts are underway to pool together the data from the existing studies of residential radon and to explore further the possibilities of deriving estimates of lung cancer risk based on cumulative residential radon exposure as recorded in glass objects, and these should provide firmer evidence. Additional insight may also arise from work aimed at further elucidating the mechanism of radon carcinogenesis (see [1] for a review). To complement these scientific endeavours additional economic work evaluating the cost-effectiveness of various intervention strategies is desirable.

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Is indoor radon linked to leukaemia in children and adults? - A review of the evidence

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Abstract

The evidence linking indoor radon exposure to childhood and adult leukaemia is reviewed. At the UK average indoor exposure of 20 Bq m^{-3} , it is estimated that the radon derived equivalent dose accrued to the fetus is $106 \mu\text{Sv}$. The equivalent dose rate to adult bone marrow is $\sim 130 \mu\text{Sv y}^{-1}$. Standard radiation risk factors suggest that 5% of childhood and 4% of adult leukaemia is linked to radon at 20 Bq m^{-3} exposure. Geographical studies generally support such a link at about this magnitude. A number of case-control studies have been carried out but these in general have not had enough resolving power to determine a link between radon and leukaemia at the level suggested by radiation risk factors.

Introduction

Radon causes lung cancer in uranium miners and for many years this was the only clear example that exposure to natural ionizing radiation can lead to cancer in humans. There is now strong evidence that radon may cause lung cancer in the general population at elevated levels indoors, but whether this occurs at average domestic levels remains unproven. Information on the risk of childhood leukaemia following exposure to ionizing radiation comes from a number of sources, notably the Japanese atomic bomb survivors (BEIR V 1990). Risk assessment based on extrapolation of the Japanese data, suggests that a measurable proportion of childhood leukaemia in the population may be attributed to background radiation. If this is the case, then we have reason to assume that radon and its decay products will also cause leukaemia. Radon and its decay products, however, may be

especially important since they emit high LET alpha-radiation. Such radiation (alpha-particles) has been shown to induce both genomic instability and bystander effects in haemopoietic stem cells.

This paper will discuss the arguments that a link between radon and both childhood and adult leukaemia is expected on grounds of risk assessment and will review the attempts to establish whether such a link exists in practice. An earlier review has been given by Little (1999), and a detailed discussion may be found in BEIR VI (1999), chapter 4.

Radon derived radiation dose to bone marrow

In radiation dosimetry, considerable effort has been made to model the radon-derived dose to the lung and the risk of lung cancer (BEIR VI, 1999). Here the dose arises primarily from the inhalation of the alpha-emitting decay products ^{218}Po and ^{214}Po , which exist in air in aerosol form (Fig. 1). For leukaemogenesis the target cells are the haemopoietic stem cells which originate in the yolk sac and colonise the bone marrow during fetal development. In this case we need to consider both the behaviour of ^{222}Rn in its own right as well as that of its decay products. We also need to take account of ^{220}Rn (thoron) due to the comparatively long half-life of the decay product ^{212}Pb (10.6 h) decaying to the alpha-emitter ^{212}Po . In this case we are not interested in the details of the tracheo-bronchial deposition of inhaled radon decay products, but rather in their transport around the body, once they have entered the bloodstream (Pohl and Pohl-Rühling 1967).

When inhaled, ^{222}Rn is distributed around the body according to its solubility, which is 0.41 in blood but 16 times greater at 6.3 in body fat (Nussbaum and Hursch 1958). Following birth, fat progressively ingrows in bone marrow in the form of fat cells up to 100 μm diameter (Allen *et al.* 1995). Radon therefore dissolves preferentially in fat allowing a proportion of the alpha-particle energy from the decay of radon and its decay products to be deposited in the surrounding haemopoietic tissue. At Bristol we have carried out detailed modelling of the radon and thoron derived dose to the fetus, the child and adult. The fetal dose is particularly relevant because many if not all cases of childhood leukaemia (acute lymphoblastic leukaemia, ALL) are thought to be initiated *in utero* (Ford *et al.* 1993, 1997; Gale *et al.* 1998; Weimels *et al.* 1999).

Fig. 2 shows a histological section of fetal bone marrow taken at 35 weeks gestation. The structure of marrow spaces is unlike that in the adult and there is a complete absence of fat cells. By about 14 weeks gestation, the evolving marrow contains haemopoietic stem cells. The number density and spatial distribution of these cells in human fetal bone marrow has recently been mapped (Allen and Henshaw 2001). Fig. 3 shows a schematic diagram illustrating the natural alpha-particle irradiation of fetal bone marrow. The main contributions to radiation dose are from radon and its decay products in bone and marrow and from ^{210}Po emissions in bone. Table 1 shows estimates of the equivalent dose to fetal bone marrow during gestation at various radon concentrations. The accrued dose *in utero* at mean radon exposures of 20, 42 and 1,000 Bq m^{-3} is respectively 106, 150 and 1960 μSv .

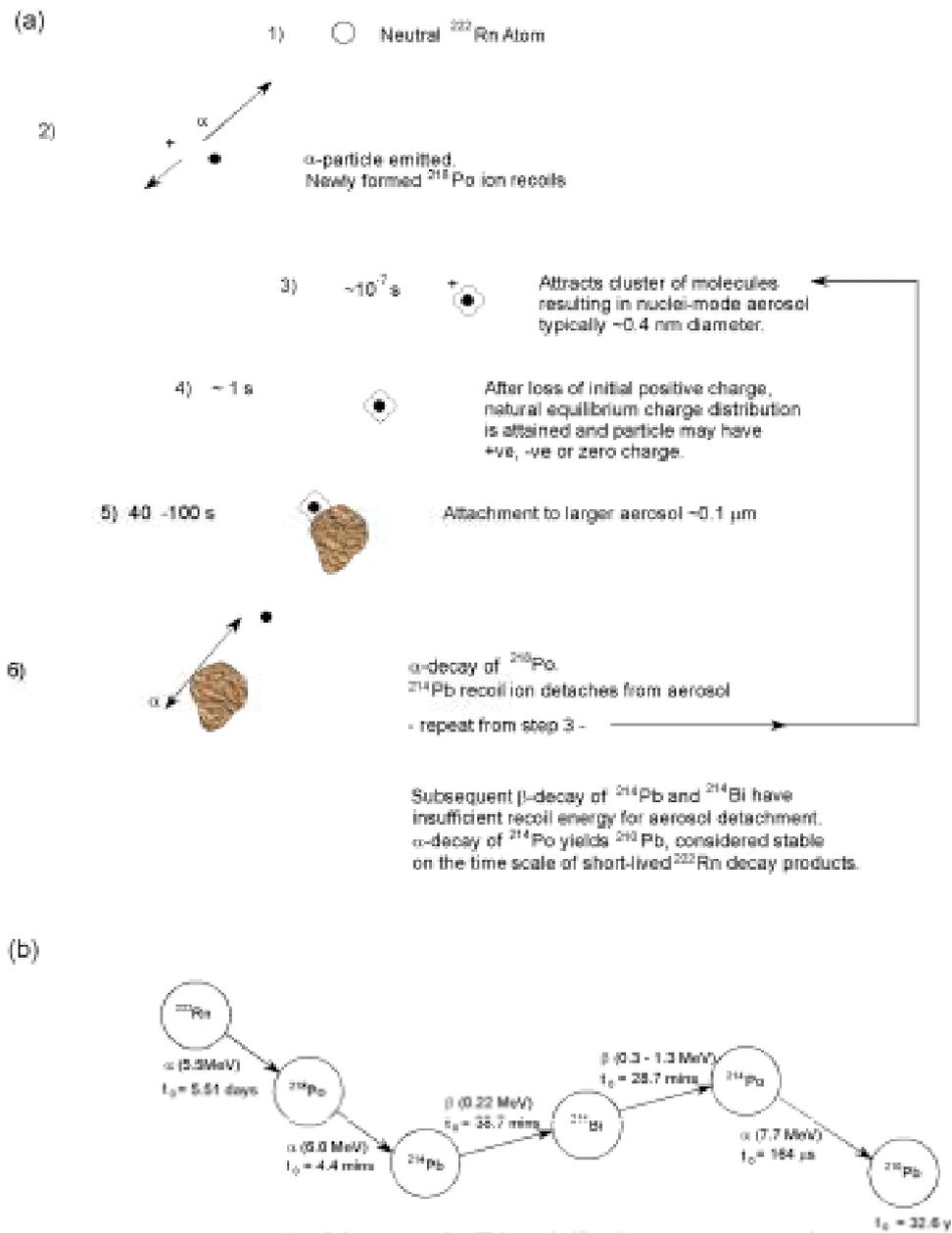


Fig. 1. (a) Growth of ^{222}Rn decay product aerosols (b) ^{222}Rn short-lived radionuclide decay chain

The above analysis concerns equivalent dose rate to haemopoietic tissue as a whole. Microdosimetric considerations suggest that a high LET alpha-particle traversing a stem cell deposits around 0.5 Gy of energy resulting in qualitatively different damage to that from low LET (gamma and beta) radiation (Goodhead 1988) and leading to around a 10% chance of cell survival. The recent evidence concerning genomic instability and the bystander effect in haemopoietic stem cells suggests that single alpha-particle traversals through cells may have a much greater effect in introducing cell damage at environmental exposures than has hitherto been assumed (Kadhim *et al.* 1992, Mothersill and Seymour 1998, Prise *et al.* 1998, Wright 1998). This is particularly important in the fetus, where only a few cells receive alpha-particle hits during gestation.

Table 1. Radon and thoron derived equivalent dose to the human fetus at three representative indoor levels: 20 Bq m⁻³ (UK average); 42 Bq m⁻³ (world average) and 1,000 Bq m⁻³. After Henshaw *et al.* (1994).

Radionuclide	Dose, μSv at			Comment
	20 Bq m ⁻³	42 Bq m ⁻³	1000 Bq m ⁻³	
Pure ²²² Rn	12	25	600	Fat free marrow
²²² Rn decay products	1	2	50	No transfer of bismuth
²²⁰ Rn decay products	23	48	1150	Transfer of ²¹² Pb
²¹⁰ Po in fetal skeleton	70	75	160	Measured at 20 Bq m ⁻³ , scaled for higher exposures
Total	106	150	1960	

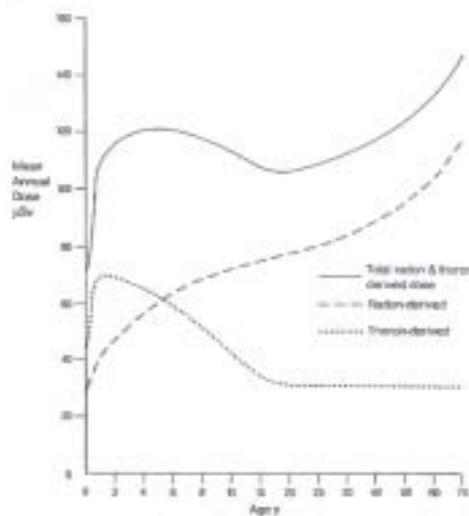


Fig. 4. Estimated mean values for the equivalent dose rate to haemopoietic marrow estimated from birth to 70 years old, at 20 Bq m⁻³ radon exposure.

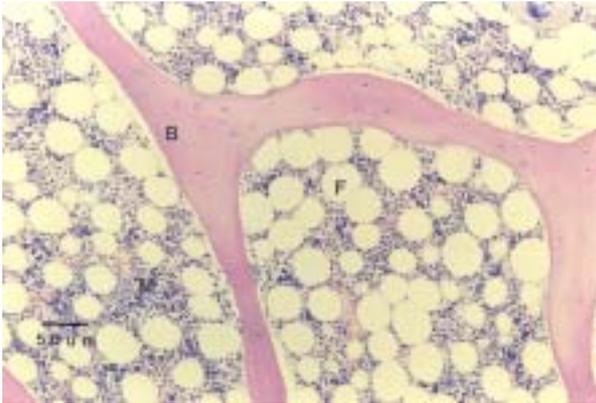


Fig. 5. Adult bone marrow in lumbar vertebra of an 81 year old female caucasian.

Initial findings

Lucie (1989) reported a statistically significant geographical association in Great Britain between domestic radon exposure and the incidence of acute myeloid leukaemia in adults. No association with gamma radiation was found. Henshaw *et al.* (1990) extended this approach using international data from 14 countries. They showed a series of correlations between domestic radon exposure, as estimated from national surveys, and the incidence of leukaemia in adults and children. In children, a significant correlation was shown for all cancers combined (Fig. 6), for leukaemia and for several specific childhood cancers. In adults, significant correlations were found for acute myeloid leukaemia (AML) and for melanoma and kidney cancer. Weak and largely insignificant correlations were found with background gamma radiation. The gradient of this correlation indicates that if causal, only 6% of all childhood cancer is linked to radon at the UK average indoor radon exposure of 20 Bq m^{-3} . The data suggest a percentage link of around 5% and 10% for childhood and adult leukaemia, respectively.

There is a further feature of these geographical associations. In the UK, Henshaw *et al* found statistically significant positive correlations for radon versus prostatic cancer and malignant melanoma, but simultaneously a statistically significant inverse (negative) correlation versus background gamma radiation. A similar though weaker effect is seen for adult and childhood leukaemia (Table 2). The correlation coefficient between radon and background gamma radiation in the UK is close to zero – i.e. they are uncorrelated. Why should the effect shown in Table 2 occur? It is generally agreed that geographical correlations should be treated with caution. Is this a mere artefact, evidence for an antagonistic interaction between radon and gamma radiation, or simply mutual confounding of the two radiation types?

The dose rate from natural background gamma radiation is such that every stem cell receives one ionizing ‘hit’ per year. On a DNA scale, ionization from gamma rays is

relatively weak and usually results in DNA single strand breaks (SSBs) which are readily repairable. On the other hand, alpha-particles are highly ionizing on a DNA scale with typically 20 ionizing events across a 2 nm DNA double strand (Goodhead 1988). This causes a double strand break (DSB), which is difficult or impossible to repair. However, at natural exposures a very small number of stem cells are traversed by an alpha-particle, and in view of the significant differences in LET a mutual (interacting) effect of alpha-particles and gamma rays is thought unlikely (D T Goodhead personal communication). On the other hand, a weak negative correlation with gamma rays could occur by confounding with radon, since the variation in gamma ray exposures across the UK is relatively small, whereas for radon far larger variations occur.

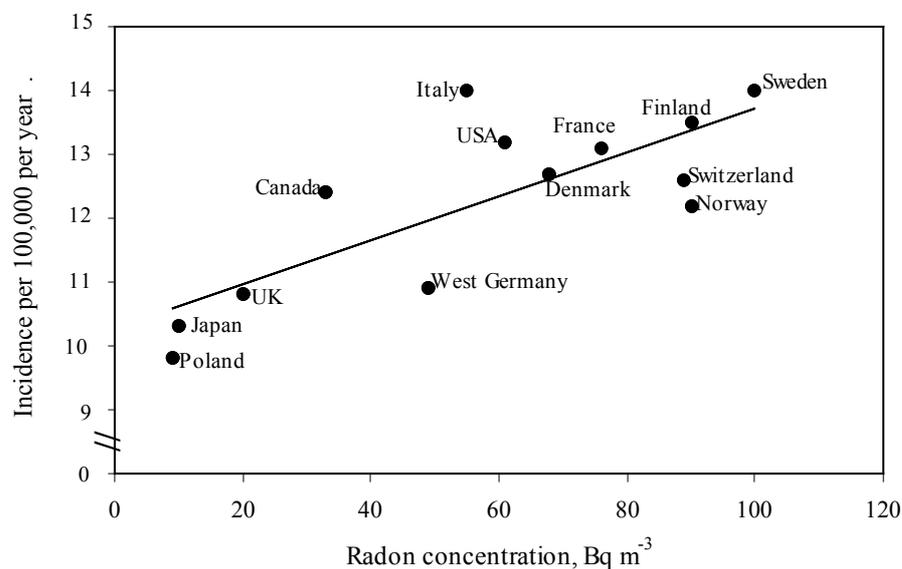


Fig. 6. International incidence of all childhood cancers combined vs. radon concentration in indoor air.

Leukaemia and radiation risk estimates

Radiation risk factors have been used to estimate the proportion of leukaemia in the population that may be linked to background radiation (COMARE 1996). Overall, 14% of childhood leukaemia has been attributed to natural high LET radiation. When account is taken of the dose to bone marrow from the various naturally occurring alpha-radionuclides (Richardson *et al* 1991, NRPB R276, 1995, Table 5.6), 5% of childhood leukaemia and 4% of adult leukaemia may be linked to radon in the UK. Coincidentally, therefore, the magnitude of the radon-leukaemia link in children derived from risk factors shows agreement with the

geographical observations (Henshaw *et al.* 1990), but for adults the magnitude of the suggested link is lower.

For childhood and adult leukaemia, these risk estimates suggest that for domestic radon exposures of 20, 100 and 200 Bq m⁻³, the respective relative risks compared to zero radon are around 1.05 and 1.04, 1.25 and 1.20, and 1.5 and 1.4. These values also indicate the statistical resolving power required for an epidemiological study designed to test the magnitude of this suggested radon link. Thus, epidemiological studies of radon and leukaemia can be seen as an experimental test of the magnitude of the radon/leukaemia link suggested by standard radiation risk factors. To be successful such studies must have the required resolving power.

Table 2. Correlation coefficients for radon contents in indoor air and outdoor gamma radiation versus prostatic cancer, malignant melanoma and leukaemia in the UK

Data set	Correlation Coefficient			
	Rn	γ-radiation	Rn/γ	
Prostate cancer mortality*				
(54 counties)				
Fractional mortality	AM	0.53 (p<0.001)	-0.49 (p<0.001)	0.73 (p<0.001)
Fractional mortality	GM	0.58 (p<0.001)	-0.55 (p<0.001)	0.83 (p<0.001)
Melanoma mortality*				
(45 counties)				
Male		0.43 (p<0.01)	-0.55 (p<0.001)	0.63 (p<0.001)
Female		0.41 (p<0.01)	-0.62 (p<0.001)	0.62 (p<0.001)
Leukemia"				
Adult AML		0.44 (p<0.05)	-0.27 (ns)	0.46 (p<0.05)
Adult ALL		0.67 (p<0.001)	-0.21 (ns)	-
Childhood ALL		0.65 (p<0.005)	-0.13 (ns)	-
All countries [†]		0.65 (p<0.02)	0.42 (ns)	0.68 (p<0.01)
5 countries [‡]		0.54 (ns)	-0.01 (ns)	0.95 (p<0.01)

* Data courtesy of the MRC Environmental Epidemiology Unit, University of Southampton. Spearman rank correlation coefficients.

[†] Data from Henshaw *et al.* (1990) Pearson's product moment correlation coefficient, (myeloid leukaemia).

[‡] Data from Henshaw *et al.* (1990) using only those countries recommended by Butland *et al.* 1990, Pearson's product moment correlation coefficient, (myeloid leukaemia).

"Data from Alexander *et al.* (1990)

AM = Arithmetic mean; GM = Geometric mean; ns = not significant at the 95% confidence level

Assessment of Radon Exposure

The methods of measurement of radon gas concentration are well established and relatively straightforward. Indoor radon levels are known to have substantial diurnal, seasonal and annual variations, and also depend on characteristics of the premises and of lifestyle such as the presence of double glazing and the use of heating. To determine the mean exposure to radon the preferred method is to use an integrating plastic track detector housed in a small diffusion chamber. For estimations of exposure with respect to the recommended annual limit (200 Bq m⁻³ in the UK), two detectors, one in the bedroom and one in the living area, exposed for three months are considered adequate. For epidemiological studies it would seem essential that the detectors be exposed for even longer periods. In the studies summarised in Tables 3 and 4 below some have measured radon in current as well as previous homes of cases and controls.

The concentration of radon gas, however, may not be an adequate measure of decay product exposure. The ratio of radon decay product concentration in air compared to the radon gas concentration (expressed in terms of the relative concentration of their alpha-particle energies, PAEC) can vary significantly, as can the fraction of decay products which are in small-ion form and unattached to aerosols (the so-called *unattached* fraction). In the case of lung dosimetry, Yu *et al* (2001) have addressed this problem by designing a detector which estimates the bronchial dose from radon decay products in air. In principle, this could also be used to estimate bone marrow dose. An additional consideration for bone marrow dosimetry is the thoron concentration in room air. This is not currently estimated in leukaemia studies.

In a number of studies, radon exposure in the homes of leukaemia cases have been estimated relative to those in neighbourhood houses (in the UK, the average radon concentration by postcode). On such a small scale these estimates are unreliable, see Fig. 7, which shows how radon concentrations may vary from less than 100 to over 1200 Bq m⁻³ in a row of identically built houses. In other studies, local geological features have been used to estimate radon exposure of leukaemia cases. Friis *et al* (1999) found that ground level radon is a poor indicator of indoor radon. However, Kohli *et al* (2000) used ground level radon as a measure of temporal exposure to radon, which demonstrated a significant association with childhood leukaemia. This study is discussed in more detail below.

Epidemiological studies of radon and leukaemia

Table 3 shows the main published papers on relationships between radon and leukaemia. The papers are listed in chronological order and include studies in both adults and children. Of the 15 studies, 10 support a link between radon and leukaemia, two have suggestive support (Forastiere *et al.* 1992, Cohen 1993) and 3 offer no support. For those with suggestive support, Cohen (1993) found a link between radon and leukaemia in women, but not in men in the USA. However, the author also found significant correlations for several cancer sites

other than lung in both men and women. For those studies offering no support, Muirhead *et al* (1992a & b) found a positive correlation with radon and a negative correlation with both indoor and outdoor gamma dose rates at county level in Great Britain, but the sign of these correlations became reversed when considered at district level within counties. This could be indicative of the "Ecological fallacy" (Morgenstern 1982) or mutual confounding of radon and gamma radiation. Richardson *et al.* (1995) using the same data set and a Bayesian analysis, found a significant correlation for cases occurring in one period but not for others. Thorne *et al.* (1996) estimated radon exposure by postcode in Devon and Cornwall. Fig. 7 shows that radon such levels are an unreliable measure of exposure in an individual case. High radon areas are known to be patchy in Southwest England.

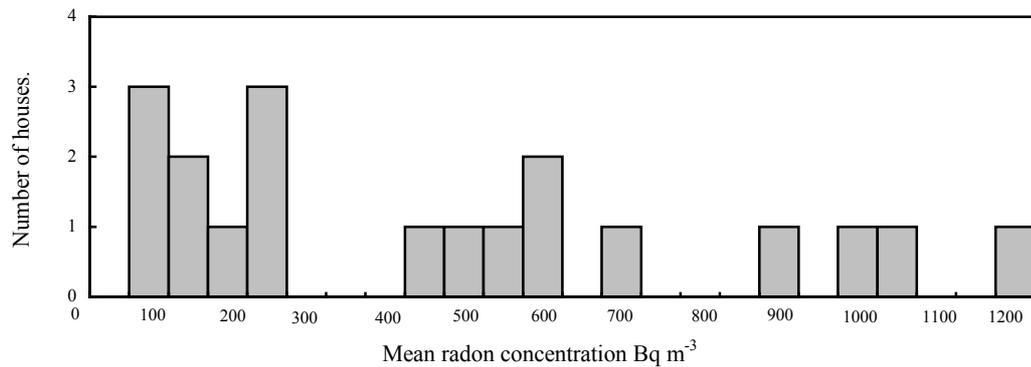


Fig. 7. Variation in radon levels in a road of 19 similarly constructed houses in Street, Somerset.

In the studies by Henshaw *et al.* (1990), international data were used to obtain good statistics in terms of number of cases and thereby minimise the effects of small-scale geographical variations in radon. Nevertheless, the majority of studies in Table 3 do support a link between radon and leukaemia. For the studies in England and Wales, Alexander *et al.* (1990) and Lucie (1990) report anomalous effects in the high radon counties of Somerset, Devon and Cornwall. Here the effects of radon and gamma radiation may be hard to separate. In the granite areas of Cornwall radon and gamma levels are both high, whereas in the porous limestone areas of Somerset radon is high but gamma radiation comparatively low.

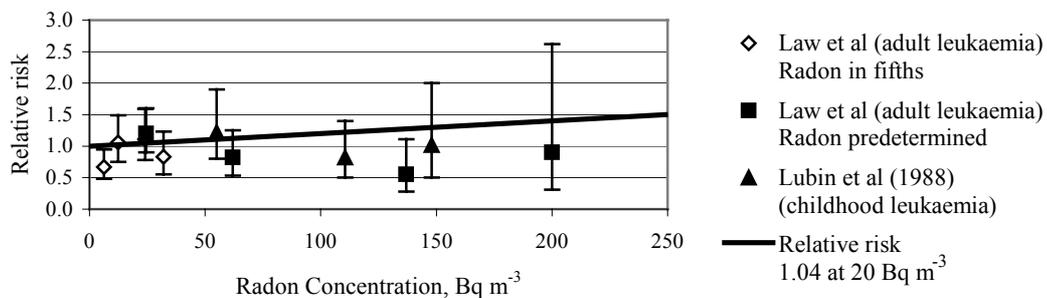


Fig. 8. Relative risk of leukaemia with increasing radon concentration in indoor air.

Table 3. Main geographical studies of radon and leukaemia

Author	Study area / Time period	Population	Exposure Assessment	Results
Lucie, 1989	Great Britain Unspecified years	Adults	UK NRPB radon survey	Correlation with AML ($r = 0.48$, $p < 0.05$)
Henshaw <i>et al</i> , 1990	14 countries 1978 – 1982	Adults and children	Population weighted mean radon exposure from national surveys	Adults: significant correlation for AML. Additional correlation for melanoma and kidney cancer. Childhood cancers: significant correlation for all cancers combined, leukaemia and certain specific cancers.
Alexander <i>et al</i> , 1990	England and Wales 1984 – 1988	Adults and children	UK NRPB radon survey	Strong correlation for several haemopoietic disorders especially AML in both adults and children.
Butland <i>et al</i> , 1990	Re-analysis of UK data in Henshaw <i>et al</i> , 1990	“	“	A significant correlation for childhood leukaemia remains. Other correlations in Henshaw <i>et al</i> are largely confirmed, but many fall below statistical significance.
Lucie, 1990	England and Wales 1984 – 1986	Adults and children	“	Correlation with childhood ALL, $r = 0.56$, $p < 0.01$. Weaker leukaemia correlations in adults.
Muirhead <i>et al</i> , 1991;1992	England and Wales 1969 – 1983	“	“	Significant positive correlations with childhood leukaemia at county level, but a negative correlation for districts within counties.
Cohen, 1993	USA unspecified years	Adults	US county radon measurements	Correlation with leukaemia in women but not in men. Significant correlation for several other non-lung cancer sites.
Richardson <i>et al</i> , 1995	Great Britain 1969 – 1983	Children	“	Significant correlation for ALL for time period 1974 – 1978, not found for other time periods.
Lyman <i>et al</i> , 1986	Florida, USA 1981	Adults	Radium in groundwater used as a surrogate for radon exposure	Correlation with radium in groundwater: (1) total leukaemia, $r = 0.56$ ($p < 0.01$) (2) AML, $r = 0.45$ ($p < 0.05$) High vs. low radium, RR = 2.0

Table 3. (cont'd)

Author	Study area / Time period	Population	Exposure Assessment	Results
Collman <i>et al</i> , 1991	North Carolina, USA 1950 – 1979	Children	Radon in groundwater used as a measure of domestic exposure.	High vs. low radon: all cancers RR = 1.23 (95% CI = 1.11 – 1.37) leukaemia RR = 1.33 (95% CI = 1.13 – 1.57)
Viel, 1993	France, 41 administrative areas 1984 – 1986	Adults	French national survey	Correlation with AML, for upper and lower tertiles: (1) univariate analysis OR = 1.11 (95% CI = 1.00 – 1.24) (2) multivariate analysis OR + 1.41 (95% CI = 1.25 – 1.62)
Forastiere <i>et al</i> , 1992	Viterbo, Italy 1980 – 1986	Adult men 1579 cases 110 mortality cases were lymphatic and haemopoietic conditions	Geological features used to assess indoor radon levels	Excess myeloid leukaemias of borderline significance: high vs. low radon, OR = 2.3, (95% CI = 0.9 – 6.1). Significant OR for kidney cancer, increase for melanoma of borderline significance
Hoffman <i>et al</i> , 1993	Ellweiler, Germany 1970 – 1989	Children	High concentrations of uranium in sub-soil	7 cases of childhood leukaemia vs 2.3 expected
Thorne <i>et al</i> , 1996	Devon and Cornwall, UK. 1976 – 1985	Children 301 cancer cases	Radon exposure estimated by postcode	Non-significant excess for AML. Significant excess for neuroblastoma.
Kohli <i>et al</i> , 2000	Östergötland, Sweden 1979 – 1995	Children 53,146 cancer cases	Ground level radon used as a surrogate for indoor radon exposure	For high radon, RR = 5.67 (95% CI = 1.06 – 43) For medium vs. low radon, RR = 4.64 (95% CI = 1.29-28.26). Stronger association with continued residence in high risk area.

Table 4. Main case-control studies of radon and leukaemia

Author	Study area / time period	Population	No. of cases / controls	Exposure assessment	Results
Stjernfeldt <i>et al</i> , 1987	Östergötland, Sweden 1980 – 1984	Children	28 / 28	For 15 cases, radon measurements in current and previous homes; for remaining cases only current home measured.	No association with radon
Wakefield and Kohler, 1991	Wessex, UK 1988 – 1991	Children	42 / 39	2 x 3 month radon measurement *	No association with radon
Pobel and Viel, 1997	La Hague, France 1978 – 1993	Young people <25 years	27 / 192	Houses made of granite, used as surrogate radon exposure	RR = 1.18 (95% CI = 1.03 – 1.42)
Lubin <i>et al</i> , 1998	9 mid-western or mid-atlantic US states 1989 – 1993	Children	638 / 620	2 x 1 year radon measurement	No consistent association
Forastiere <i>et al</i> , 1998	Central Italy 1980 – 1989	Adults	44 / 211	1 x 6 month radon measurement	OR = 0.56 (95% CI = 0.2 – 1.4)
Law <i>et al</i> , 2000	UK 1991 – 1996	Adults	578 / 983	2 x 6 month radon measurement	No association with radon

Note: In none of these situations was there sufficient resolution to detect the kind of effect predicted by standard radiation risk factors.

* 2 x 3 denotes 2 radon detectors in the home for three months

Table 4 lists the main case-control studies of radon and leukaemia. Pobel and Viel (1997) found a statistically significant association between houses made of granite and granite areas versus leukaemia in young people <25 years. For the remainder, none has sufficient resolving power to detect a link between radon and leukaemia at the level suggested by radiation risk factors. This is illustrated in Figure 8 for the data of Lubin *et al* (1998) and Law *et al* (2000). These studies indicate that in countries such as the UK, where domestic exposure is relatively low, radon poses at most a small public health risk for leukaemia. Additional data for radon and background gamma radiation versus leukaemia are expected to be available from the UK Childhood Cancer Study is due to be published during 2002.

Finally the Swedish study by Kohli *et al* (2000) shown in Table 3 warrants special mention. The authors carried out a temporal analysis of childhood leukaemia in different areas, assessing radon exposure from the Geological Survey of Sweden risk classification. The authors found evidence that children born and continuously living in areas with normal to high levels of radon have a higher than normal incidence of ALL. They found a stronger association with continued residence than with place of birth. For the 53,146 cases of childhood malignancy, SMRs for ALL among children born in high, normal and low risk areas were 1.43, 1.17 and 0.25, respectively. The relative risk for the normal and high-risk group as compared with the low risk group was 4.64 (95% CI 1.29 – 28.26) and 5.67 (95% CI 1.06 – 42.27). The authors argue that although this is a geographical study, it was not based upon aggregated data but thorough individual information. They further argue that ground radon is a better temporal measure of total exposure than after-the-event radon measurements in the home. Notwithstanding the findings of Friis *et al.* (1999) which concerned the relationship between contemporaneous ground and indoor radon, we have sympathy with this view. As indicated earlier there is strong evidence that the initiating step in childhood leukaemia is present at birth. Apart from possible genetic factors, this emphasises the importance of *in utero* exposure and therefore the movements of the expectant mother. After-the-event radon measurements in the home may not adequately describe exposure conditions during initiation and progression of childhood leukaemia.

Discussion and Conclusion

Geographical studies show a degree of consistency of support for a link between radon and leukaemia in both adults and children at about the level predicted from standard radiation risk factors. It is generally agreed that geographical studies should be treated with caution. A number of case-control studies of radon and leukaemia have been carried out of which one has reported a link with radon, when the presence of granite is used as a surrogate for exposure. Other studies have reported no link, but none of these had sufficient resolving power to detect the excess risk suggested by the radiation risk factors. Kohli *et al.* (2000) showed a strong association between radon and childhood leukaemia especially with continued residence in areas of high radon levels. Although this was a geographical study, it was not based upon aggregated data but thorough individual information. The authors argue

that ground radon is a better temporal measure of total exposure than after-the-event radon measurements in the home.

Further studies of radon and leukaemia are warranted both to test the predictions of radiation risk analysis and to help determine whether the phenomena of genomic instability and the bystander effect impact on risk at natural exposures to high LET radiation. They are also warranted in view of the public health implications in areas and countries with high radon exposures. Future studies must address resolving power and the question of how best to assess exposure to radon, thoron, their decay products and gamma radiation at the time of initiation and progression of leukaemia.

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Ecological analysis: nasopharyngeal carcinoma and multiple sclerosis versus radioactive elements

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Abstract

Comparisons of epidemiological and geochemical maps revealed that in a region in South-Eastern China exceptionally high rates of *nasopharyngeal carcinoma* (NPC) coincide with anomalous contents of U and Th in soils. In Norway statistical analyses show that high rates of *multiple sclerosis* (MS) are associated with high levels of Rn in indoor air. Based on these observations it is suggested that high contents of radioactive elements in soil or air may be risk factors in NPC and MS. Some general comments are given on the use of ecological analysis in epidemiology together with a discussion of possible pathways of chemical substances from environment to human beings. It is concluded that empirical data have a potential for disclosing hitherto unknown geomedical associations, which may lead to the formulation of etiological hypotheses.

Introduction

Many examples of correlations between diseases and the chemical environment have been disclosed throughout the history of medicine, of which the causal ones between dental health and fluorine and between goitre and iodine probably are the best known. In our times there is a potential for finding additional association of this type, since new data on the chemical properties of the environment are being disclosed in many countries. For example, radiation protection authorities study spatial distributions of the radon content in indoor air. Such data have long been of interest in connection with incidence of lung cancer. Geological surveys and private industry perform geochemical mapping based on chemical analyses of samples of a variety of materials, such as waters, soils and stream sediments. This type of mapping is normally used as a tool in mineral exploration, but since many elements are often determined, the data may also be applied in other fields, among them epidemiology. By comparing spatial distribution patterns of chemical elements with corresponding data for the occurrences of endemic diseases, associations may be found that could lead to the formulation of new etiological hypotheses.

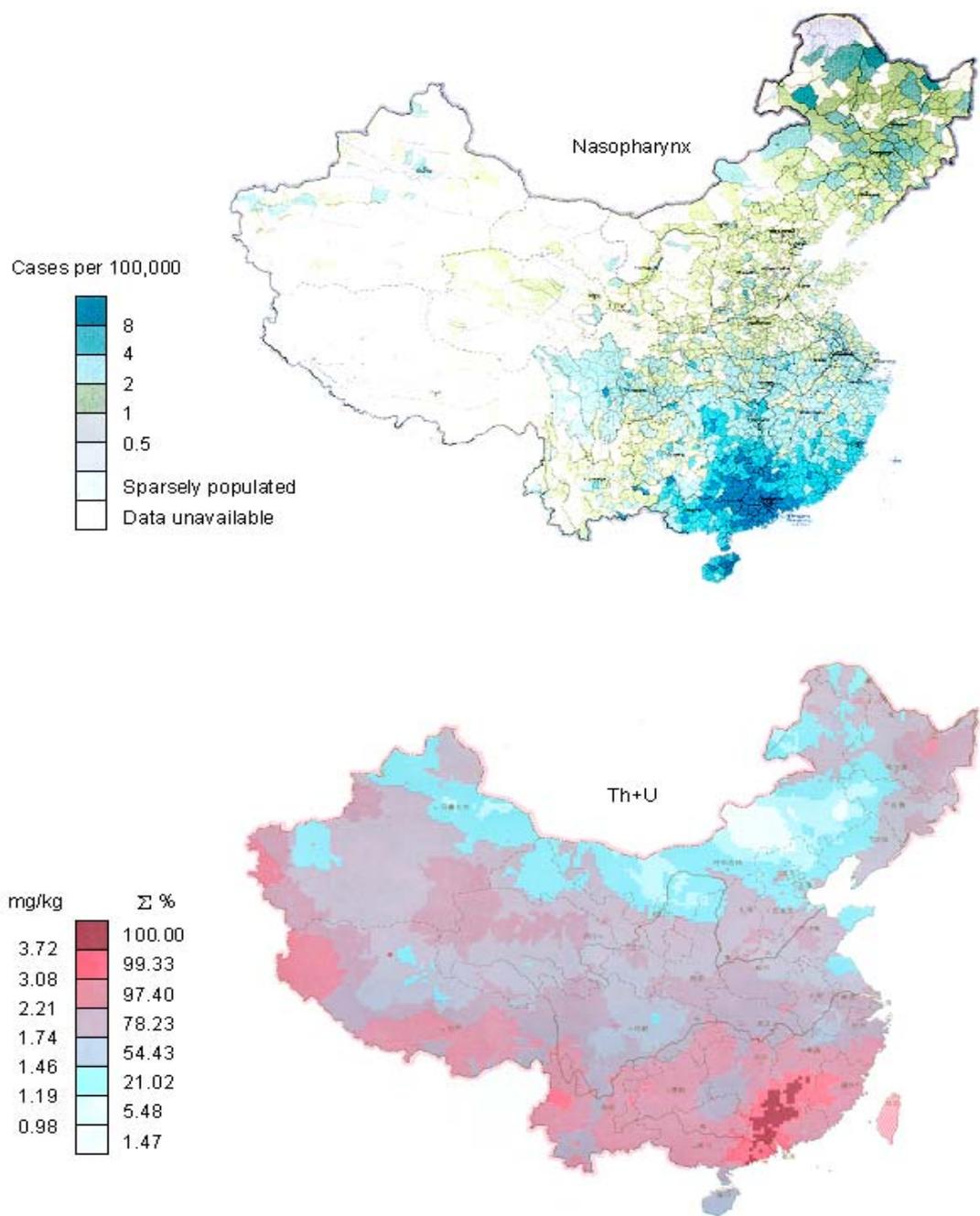


Fig. 1. Upper part. Mortality of cancer of the nasopharynx in men in China 1973-1975. After Li et al. (1979). Lower part. Concentrations of the sum Th+U in soils from the B horizon, China. The raw data for 4000 samples are smoothed by the Kriging technique. After (Chunjiang et al. 1994).

This paper reports on two such cases involving radioactive elements, Case History 1 about *nasopharyngeal carcinoma* (NPC) in China, and Case History 2 about *multiple sclerosis* (MS) in Norway. Towards the end of the paper some viewpoints are given on the use of ecological analysis in epidemiology and of possible pathways from environment to human beings.

Case History 1. Nasopharyngeal carcinoma (NPC) in China

NPC is a malignant disease in the respiratory tract. The disease is very rare in most places, but in parts of South-Eastern China it is the most common type of cancer with incidence rates about 100 fold those in most Caucasian populations (Muir et al.1987). The aetiology of NPC is not completely understood, but it is thought to be determined by an interplay of three factors, namely (1) a genetic element, (2) the Epstein–Barr virus and (3) one or more properties of the environment (Ho 1972). Many attempts have been made to find the environmental agents. As a result of this research consumption of salted fish and other kinds of preserved foods has attracted attention (Yu 1990). However, convincing evidence that these are the only environmental factors of interest has not been produced. It is, therefore, still desirable to look for additional possibilities.

Epidemiological maps of China show that the NPC rates depict an irregular pattern with exceptionally high rates in South East China in relation to those in the rest of the country. Comparison of the epidemiological maps for NPC with maps showing the contents of Th and U in soils, reveals that the areas with the highest NPC rates in the south-east of the country also have anomalously high contents of radioactive elements in soil, especially Th, but also U (Fig. 1). The area with high NPC is further characterized by low contents of Mg, Ca and Sr (not shown here), see Zeng et al. (1994), Bølviken et al (1997); Bølviken (2000).

Case History 2. Multiple sclerosis (MS) in Norway

MS is a serious disorder that implies demyelination in the central nerve system resulting in motor weakness. Norway belongs to the countries where MS is most prevalent. The aetiology of MS is not completely understood, but it is widely accepted as being multifactorial, i.e. due to three main types of agent: (1) a genetic element, (2) a virus and (3) one or more external environmental factors (Mathews et al. 1991)

Westlund (1982) published rates for the sum of MS-related deaths and disabilities for Norwegian municipalities . Based on these data, Brørvik (1984) estimated age and sex adjusted total rates for each of 73 rural municipality aggregates spread over the country. Bølviken (1998) and Bølviken et al. (1997, 2003) compared these rates with various environmental parameters, of which contents of Rn in indoor air and the fall out of marine salts are referred here.

Data for municipality aggregates were used in these comparisons, because the population of some of the municipalities in Norway are too small to produce reliable data for rare

diseases. Only rural municipalities were used in order to emphasize the effects from natural conditions and reduce those from socio-economic factors such as moving.

The MS incidence rates in the rural municipality aggregates depict a systematic distribution pattern (Fig.2), showing low incidences along the coast and in Northern Norway, and high incidences in the inland of Southern Norway east of the main mountain range.

The concentration of Rn in indoor air has been determined by Strand et al (1991) in 7500 randomly selected Norwegian houses using the nuclear track method for 6-month periods during 1987 to 1989. From these data the arithmetic mean of Rn concentrations (Bq/m^3) were computed for each of the 73 rural municipality aggregates (Fig 3).

Municipal aggregate values for annual fallout of Mg were calculated from precipitation data published by the Norwegian Institute of Meteorology (Førland 1993) and interpolated values of Mg concentrations in precipitation recorded at 40 stations distributed throughout Norway (NILU 1995) (Fig. 4).

The statistical co-variations between the epidemiological and the environmental data were analysed with a method of spatially moving correlation (Bølviken et al. 1997). A circular window is drawn around an observation point on a map of digitised data in such a way that it encompasses the $n-1$ nearest points on the map (Fig. 5). The Spearman rank correlation coefficient for epidemiological versus environmental data is then calculated for the n observation points within the window. The obtained value is plotted as a symbol located at the central point of the window. A new circular window encompassing the $n-1$ closest neighbours is then defined around another observation point on the map, and the correlation coefficient is calculated and plotted in the same way as for the first window. This procedure is repeated for all possible window positions (in this case 73). The resulting map shows the spatial distribution of the correlation coefficient for the mutually overlapping windows. At heterogeneous density of the observation points the size of the circle will vary over the map, but the degree of freedom ($n-2$) will be constant for all windows independent of position. The number of observation points (n) within the window is chosen by the operator as a compromise between a good resolution (low n) and an acceptable precision (high n). In this case n was chosen to be 25. Significance tests of the obtained correlation coefficients were done by comparing with results of 1000 simulations using permuted data..

In the western parts of southern Norway there are significant positive correlations ($p < 0.05$) for MS versus the contents of radon in indoor air (Fig 6), and inverse (negative) correlations ($p < 0.05$) for rates of MS versus fallout of Mg (Fig 7). (Bølviken et al. 2003). There are no similar correlations in Northern Norway.

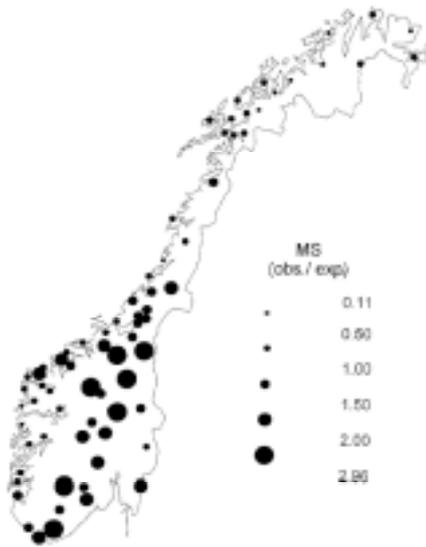


Fig. 2. Occurrence of multiple sclerosis in 73 rural municipality aggregates in Norway. After Westlund (1982) and Brørvik (1984)

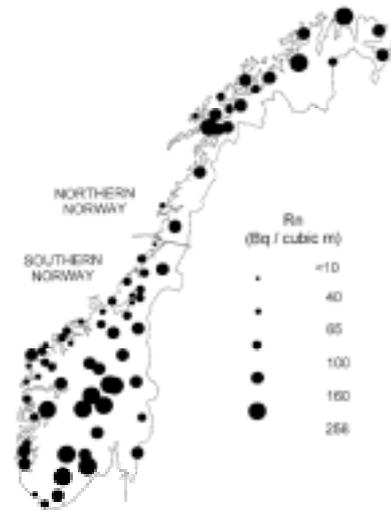


Fig. 3. Average contents of Rn in indoor air in 73 rural municipality aggregates in Norway. After Strand et al. (1991)

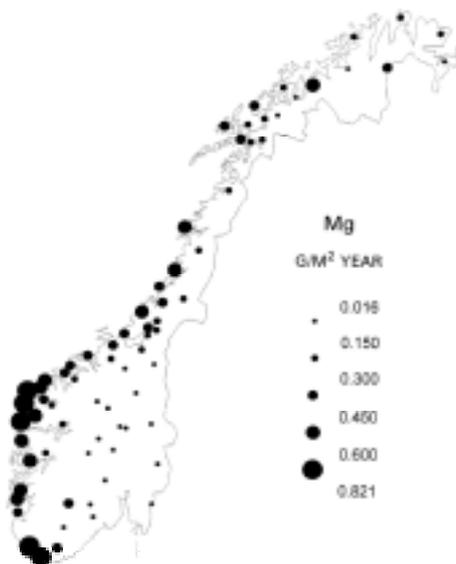


Fig. 4. Estimated fallout of Mg in 73 rural municipality aggregates in Norway. After Førland (1993) and NILU (1994).

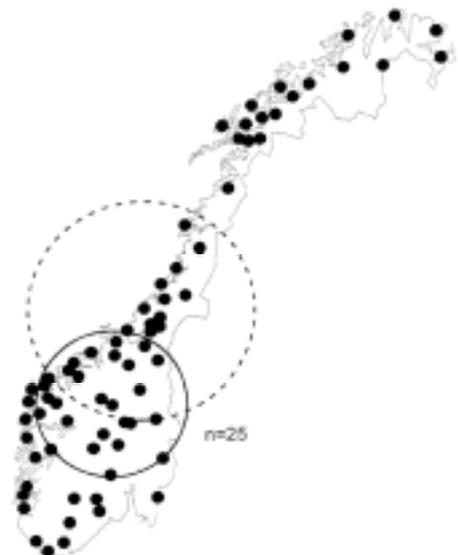


Fig. 5 Principles of spatially moving pairwise correlation. The correlation coefficient is estimated for each position of a window, which is moved stepwise over the map. The number (n) of observation points within the window (in this case 25) is kept constant.

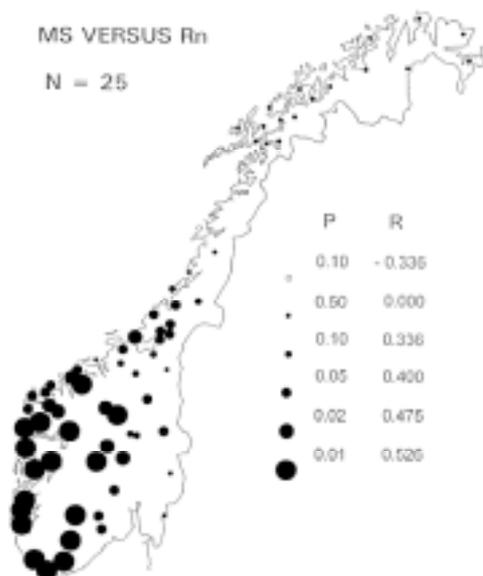


Fig. 6. Spatially moving correlation for municipal rates of multiple sclerosis (Westlund 1982) versus Rn in indoor air (Strand et al. 1992). See also Figs. 2 and 3.

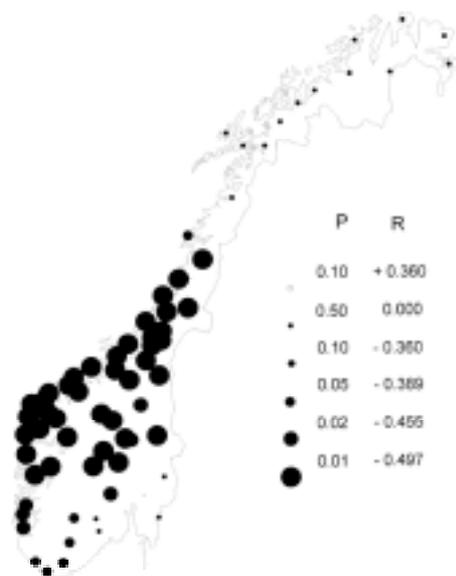


Fig. 7. Spatially moving correlation for municipal rates of multiple sclerosis (Westlund 1982) versus atmospheric fallout of Mg (Førland 1993 and NILU 1994). See also Figs. 2 and 4.

Comments on the observed associations

The associations found for NSP in China and MS in Norway have certain similarities. In both cases high incidence rates of the disease coincide with high levels of radioactive elements and low levels of Mg. These features are no proof of causal relationships, but suggest, nevertheless, that a possible role of these elements in the development of the diseases should be further studied. Rn may in both cases be a harmful agent, while a possible beneficial effect of Mg could perhaps be an indirect one.

Låg (1968) showed that in Norway fallout of airborne marine elements, such as Mg, might replace exchangeable alkaline earths in the upper humic layer of soils, producing a pattern of increasing Ca from coast to inland. Reimann et al. (2000) demonstrated similar effects of Mg on Ba contents in soil, and Bjerck et al. (1999) indicated that ion exchange between marine cations and Chernobyl-derived ^{137}Cs is more pronounced along the coast than inland. The Rn progeny Ra may perhaps behave similarly to the mentioned heavy alkalis and alkaline earths.

Problems involved in the use of ecological analysis

It has been shown that the results of ecological analysis for groups of persons are not always valid for individuals. This is the so-called ecological fallacy; see for example Morgenstern (1982). In addition, non-considered parameters (confounders) might dominate in the analysis. Many researchers, therefore, state that ecological analysis may be misleading and should be used with great care, preferably only after an etiological hypothesis is formulated.

Some comments to these objections are given below:

- (1) Medical history has several cases of a successful early application of ecological analysis. The classical example is Snow's work in London in the 19th century. Snow plotted the known cases of cholera in the city on maps and pointed thereby to the existence of a waterborne pathogenic factor, that consequently could be offset by dismounting certain water pumps (Rosenberg 1962).
- (2) It is better to run the risk of an ecological fallacy than to lose new important information. Serious consequences of possible ecological fallacies may be avoided by suitable follow-up work (e.g. case control studies) before any intervention is realized. Possible confounders may then also be defined, leading to the disclosure of the real factors.
- (3) Ecological studies should be used to generate hypotheses, rather than to test these. Ecological fallacies and confounders may even be a greater problem in the testing than in the formulation of a hypothesis, because in the testing, corroboration of a suggested hypothesis may easily be misjudged as proof of causality.

Possible pathways from environment to humans

The natural environment may influence the health status within population groups in many different ways. A list of some important mechanisms is given below. However, the combined effect of these mechanisms may be very complex. The individual cause-and-effect functions are not-linear, since various agents may act synergistic or antagonistic in relation to each other, depending on the circumstances.

- (1) The health of human beings may be influenced through the intake of drinking water, which may contain a variety of harmful or beneficial constituents of local origin, such as particles, dissolved salts and micro-organisms.
- (2) Food consumption is another pathway from environment to humans. This environmental impact is greatest in populations living close to nature, but even in industrialized countries some foodstuff such as vegetables, fruit and milk may be produced locally in the region of consumption, reflecting properties of the local geochemistry.
- (3) Inhaled air contains dust particles and vapour with dissolved salts. Some of this material could be anthropogenic, but in many places the bulk may be natural, reflecting

the composition of near and remote waters and other geological and biological materials. Constituents in the air may be taken up directly through skin and lung epithelium or enter the digestion tract after having been retained in respiratory organs and moved up through the trachea (Wagner 1980).

- (4) Intake of soil is an important pathway from the environment to grassing animals. It has been shown, however, that accidental or deliberate ingestion of soil (geophagia) is a realistic possibility also for human beings.(Thornton 1984, Smith 2001).
- (5) Natural ionizing radiation may influence the health of human beings depending on local conditions, since the content of radioactive elements in the basement, the water and air vary both locally and regionally. In countries with climates where heating is common, the indoor air may be enriched in Rn to concentrations far above the natural ones, see for example Strand et al. (2001).
- (6) The natural environment may influence the health of human beings through complex pathways, for example through intermediate hosts of harmful micro-organisms. Malaria and bilharzias provide well-known examples of such problems.
- (7) Viruses are involved in the pathogenesis of many diseases. Some virus may have an impact on human beings early in life, and then a latent period during which it may be reactivated by various factors, such as stress and ultraviolet radiation (Oakley et al. 1997). This points to the possibility that latent virus may be reactivated by various properties of the natural environment

Conclusion

Empirical data indicate that the field of geomedicine (also called *medical geology*) has a potential for disclosing hitherto unknown associations between spatial distributions of diseases and qualities of the environment. Such associations may animate new perspectives in epidemiological research.. Even though associations alone cannot prove any causal relationships, they may lead to the generation of etiological hypotheses, which can be tested, by case control studies or other epidemiological methods.

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Cancer Incidence among Norwegian Airline Crew

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Introduction

For many years there has been a discussion on small doses of ionizing radiation and health effects. Results from epidemiological studies are needed for that discussion. But there are difficulties in performing such studies, some of the interesting diseases are very rare in the general population and large populations are needed for demonstrating small effects. Another problem is estimation of doses, it may be difficult to make reliable estimates of the doses for the persons included. One way of achieving materials are to look at groups that have some occupational exposure to ionizing radiation. Airline crew is such a group.

Jet planes were introduced in commercial air traffic around 1960. Since then many new types of jets have been introduced and an increasing part of the routes are served by jet planes. These have increased cruising altitude compared to the propellers. This means that aircraft crew by time have been more exposed to cosmic radiation at work. The exposure is within the limits of the regulations for occupationally exposed persons and the annual doses may be compared to that of natural background radiation. But even if the doses are very small it may be interesting to study cancer incidence among airline crew to have empirical input to the discussion of health effects of low doses of ionizing radiation.

In later years there have been some studies of cancer incidence among airline crew (Pukkala et al. 1995, Grayson et al. 1996, Band et al. 1996, Gundestrup et al. 1999, Rafnsson et al. 2000, Rafnsson et al. 2001). Among Finnish cabin attendants an excess risk of breast cancer was found (Pukkala et al. 1995). In the Canadian and Danish studies there were indications of an excess leukemia risk for pilots (Band et al. 1996, Gundestrup et al. 1999).

The present project has been a collaboration between three different institutions. The results we present have been published elsewhere (Tveten et al. 2000, Haldorsen et al. 2000, Haldorsen et al. 2001). The first article presents the procedure for estimation of doses for pilots. The others give results on cancer incidence among Norwegian pilots and cabin crew.

Material

The cohorts were established with information from the files of the Civil Aviation Administration that authorize both pilots and cabin crew for serving on a commercial airplane. More details were found on the aviation career of the pilots that are to renew their licence every 6 or 12 months. Among pilots are also included flight engineers and helicopter pilots. The pilot cohort included all persons who had valid licenses as commercial pilots between 1946 and 1994. For the pilots the files contained information of type of license, type of aircraft, dates for renewal of license, cumulative flight hours and information on smoking habits. The flight hours recorded are the so called block hours, measuring the time from leaving a gate to entering the gate at arrival. The cabin cohort included all persons with a cabin crew license between 1950 and 1994. The cabin crew renew their licence every fifth year, every second year before 1983.

For each pilot we knew annual block hours and what type of plane they were flying. If we had dose rate per hour for each plane, this could be multiplied by block hours to produce an estimate of annual dose. Time tables of SAS gave all flight legs served and type of planes that were used. For each type of plane the distribution of time on different flight leg duration was estimated. A selection of routes representing different flight leg durations was found. For these routes the doses were estimated by CARI, a computer program from Federal Aviation Administration in the United States. Important input to this program is the flight profiles on the various routes. Members of the Pilots Association were consulted about flight profiles. The doses from the program were weighted by the distribution for time on different flight leg durations to produce an average dose rate for each plane. For planes not used by SAS a simpler method was used. For these, members of the Pilots Association suggested typical routes where the planes had been used and CARI estimates were made for these. The estimated dose rates for the planes varied between 0.03 $\mu\text{Sv/h}$ to 4.3 $\mu\text{Sv/h}$. The average block hours per year was below 500, and the estimated annual doses for pilots were very seldom above 2-3 mSv.

To keep track of persons after they were included in the cohorts, we used the population registries of Norway. These also supplied the fertility history of women born after 1934. The Cancer Registry of Norway is population-based and have registered incident cases of cancer since 1953. All inhabitants of Norway have since 1960 had a unique identification number, and this was used for linkage of the data sources.

Results

About 3700 men were included in the cohort of pilots, data on 63 female pilots are not presented due to the small number. The cohort of cabin crew is about the same size as the pilots. The follow-up included more than 70 000 person years for both cohorts. For pilots this

is slightly above the corresponding Canadian and Danish studies. Our cabin cohort is about 3 times larger than the Finnish one. In both cohorts there were some emigration. Individual follow-up of these persons stop at the date of emigration.

For cancer incidence we report the number of observed cases in the cohorts, the expected number of cases given the person years in the cohort and incidence rates by age and calendar periods in the general population. Standardised Incidence Ratio (SIR) is computed as ratio of observed to expected. For the SIR a 95% confidence interval is presented. For all cancer combined, only men serving as cabin crew had a cancer incidence significantly different from that of the general population (Table 1).

Given the exposure to cosmic radiation, the cancer sites most convincingly related to ionizing radiation should be considered. That is leukemia when excluding chronic lymphatic leukemia, thyroid cancer and breast cancer among women.

For the cohorts combined there are 3 cases of leukemia versus 5.4 expected (Table 1). Combining the cohorts we also found less cases than expected of thyroid cancer (Table 1). The comparison to the general population should be supplemented with analyses within the cohorts. For the pilots we have estimates of dose and can use this in the tabulation. Combining leukemia and thyroid cancer, the cases are not found in the upper categories by dose (Table 2).

For the cabin crew we have to use duration of employment as a proxy for exposure. There is an increase in SIRs by duration but this is far from significant since it based on only 5 cases (Table 3).

Leukemia and thyroid cancer are rare diseases and more informative might be the figures for breast cancer. There were 38 cases versus 34.0 expected (Table 1). There was no indication of an increasing trend in SIRs by duration of employment (Table 3).

Number of children and age at first birth are well known risk factors for breast cancer. In an internal analysis we adjusted for these two variables as well as age and calendar period. But the estimates of the effect of duration of employment changed little from the external analysis. There was no effect of length of employment before 26 years old, a variable included to test harmful effect of exposure at young age (Table 4). The analysis was restricted to persons with complete information on fertility and included 30 cases of breast cancer.

Looking at the types of cancer more closely related to ionizing radiation we did not among Norwegian airline crew find any effect of their exposure to cosmic radiation.

But for both cohorts we found excess risk for malignant melanoma and non-melanoma skin cancer (Table 1). This has also been found in other studies of airline crew. Ionizing radiation has been very seldom discussed in connection to malignant melanoma, it has been discussed in connection to non-melanoma skin cancer but usually for much higher doses than airline crew experience. Solar radiation is a risk factor for these cancers. We do not have data to prove that airline crew are more exposed to the sun at their leisure time than the general population. Later studies in Norway indicate an excess risk of these cancers in the upper social class, presumably connected to leisure time activities. So far leisure time activities are our suggestion for explanation of the excess risk for these cancers.

Even if Civil Aviation Administration had taken care of data back to 1950, the precision in our results are limited. Studies on cancer incidence among aircraft crew have also been undertaken in the other Nordic countries. Both for pilots and cabin crew there will be performed pooled analyses of the Nordic material.

There will also be a European study, but since some of the countries do not have a national registration of incident cancer cases, that study will be based on cause of death.

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Table 1. Cancer incidence among Norwegian airline crew				
	Observed	Expected	Standardised incidence ratio	95% confidence interval
All sites combined				
Pilots, men	200	188.8	1.06	0.9-1.2
Cabin crew, men	52	30.4	1.71	1.3-2.2
Cabin crew, women	127	117.3	1.08	0.9-1.3
Leukemia (excluding chronic lymphatic leukemia)				
Pilots, men	1	3.3	0.3	0.0-1.7
Cabin crew, men	1	0.6	1.8	0.0-10.1
Cabin crew, women	1	1.5	0.7	0.0-3.8
Thyroid cancer				
Pilots, men	2	1.5	1.3	0.2-4.7
Cabin crew, men	0	0.3	0.0	0.0-14.5
Cabin crew, women	3	4.1	0.7	0.2-2.1
Breast cancer				
Cabin crew, women	38	34.0	1.1	0.8-1.5
Malignant melanoma				
Pilots, men	22	12.3	1.8	1.1-2.7
Cabin crew, men	6	2.0	2.9	1.1-6.4
Cabin crew, women	19	11.2	1.7	1.0-2.7
Non-melanoma skin cancer*				
Pilots, men	14	5.9	2.4	1.3-4.0
Cabin crew, men	9	0.9	9.9	4.5-18.8
Cabin crew, women	5	1.7	2.9	1.0-6.9

* Basal cell carcinomas not included

Table 2. Trend by cumulative dose for leukemia* and thyroid cancer combined, pilots				
	Observed	Expected	Standardised incidence ratio	95% confidence interval
(0-1) mSv	2	2.6	0.8	0.1-2.7
[1-10) mSv	1	1.1	0.9	0.0-4.9
[10-20) mSv	0	0.7	0.0	0.0-5.1
[20+) mSv	0	0.3	0.0	0.0-11.1

*Excluding chronic lymphatic leukemia

Table 3. Trend by duration of employment, cabin crew				
	Observed	Expected	Standardised incidence ratio	95% confidence interval
Leukemia* and thyroid cancer combined				
< 5 years	2	3.2	0.6	0.1-2.2
5-14 years	2	2.4	0.8	0.1-3.0
15+ years	1	0.8	1.3	0.0-7.4
Breast cancer (women only)				
< 5 years	19	15.7	1.2	0.7-1.9
5-14 years	14	13.0	1.1	0.6-1.8
15+ years	5	5.3	0.9	0.3-2.2

*Excluding chronic lymphatic leukemia

Table 4. Adjusted* rate ratios for length of employment and length of employment before the age of 26 from multivariate analysis of breast cancer incidence		
Length of employment (years)	Rate ratio	95% confidence interval
Total		
0-4	1.0	Reference
5-14	1.1	0.4-2.6
15+	1.0	0.3-3.0
Before age 26 years		
0	0.4	0.1-1.9
(0, 1) years	1.4	0.4-4.5
1, 2	0.9	0.2-2.8
2, 3	1.2	0.5-3.0
3+	1.0	Reference

*Adjusted for attained age, calendar period, number of children and age at first birth.

Should Radon be Removed from Homes? A Cost-effect Analysis.

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Radon is a radioactive gas that may leak into buildings from the ground. Studies of underground miners have shown that radon exposure is a risk factor for lung cancer. Case-control studies from the general population indicate a risk also at the lower radon levels found in homes. The radon concentration in homes may be reduced by simple ventilation procedures, or by more costly changes in the construction.

An intervention against radon exposure in homes may consist of locating homes with high radon exposure (above 200 Bq m⁻³) and improving these, and protecting future houses. The purpose of this paper is to calculate the costs and the effects of this intervention.

We performed a cost-effect analysis from the perspective of the society, followed by an uncertainty and sensitivity analysis. The direct costs consists of measurement, improvement and added construction costs in future homes, minus treatment costs for those that would become ill without the intervention. The number of lung cancers caused by radon exposure was calculated from the observed number of lung cancers times the attributable fraction of lung cancers due to radon. The latter was calculated from the relative risk of lung cancer for a given radon level and the number of homes with this radon level. The relative risk of lung cancer is assumed to increase linearly with the radon level, with RR=1.23 (range 1.05-1.6) at 150 Bq/m³. The distribution of radon levels in Norwegian homes is lognormal with median=38 Bq/m³, mean=74.5 Bq/m³, and 7.6 % above 200 Bq/m³. All costs and effects are presented as total present values discounted at 3% per year. In the uncertainty analysis, the simultaneous effect of uncertainty in the parameters on the cost-effect ratio is estimated, as well as the sensitivity of the cost-effect ratio towards variation in each parameter.

The preventable attributable fraction of radon on lung cancer was 3.8% (95% uncertainty interval: 0.6%, 8.3%). In cumulative present values the intervention would cost 238 (145, 310) million \$ and save 892 (133, 1981) lives, each life saved costs 0.27 (0.09, 0.9) million \$. The cost-effect ratio was sensitive to the radon risk, the radon exposure distribution, and the latency period of lung cancer. Together these three parameters explained 90% of the variation in the cost-effect ratio.

The uncertainty in the estimated cost per life is large, mainly due to uncertainty in the risk of lung cancer from radon. Based on estimates from road construction, the Norwegian society has been willing to pay 1.4 million \$ to save a life. This is above the upper uncertainty limit of the cost per life. The intervention against radon in homes therefore seems recommendable.

Radioactive Deposits Associated with Gas Condensate Production and Treatment

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Abstract

The existence of an "invisible" ^{210}Pb and progeny containing scale in tubes, valves, separators, tanks etc. is generally little known in the petroleum industry. Radioactivity above the exemption level has however been measured in such equipment in the North Sea and elsewhere. A general survey program for ^{210}Pb and progeny should be implemented in order to reveal the extent of the problem.

Introduction

Production and enrichment of naturally occurring radioactive material (NORM) in the petroleum industry has attracted increasing attention during the last 15 years as a potential health hazard problem. The radioactivity is usually associated with precipitates (scales) and sludge in production tubing, pumps, valves, separators, settling tanks etc. wherever water is being transported or treated. ^{226}Ra and ^{228}Ra are the most well known radioactive constituents in scale. This presentation will focus on a different type of low specific activity deposit, "lead scale". Lead scale contains the long-lived radionuclide ^{210}Pb (half-life = 22.3 y) and the shorter-lived progeny ^{210}Bi and ^{210}Po .

Formation and transport of lead scale

Low specific activity deposits containing ^{210}Pb have been found in connection with gas production in the Norwegian sector of the North Sea. Lead deposits can be transported through the production system either supported by the noble gas ^{222}Rn (where ^{210}Pb is produced in the decay of ^{222}Rn) or unsupported (as ^{210}Pb).

Deposits formed by the first mechanism are most likely to be found at locations where the gas is retained for some time and in equipment that only treats gas or condensate. This may result in transport of ^{222}Rn (and thereby ^{210}Pb) over long distances. The deposit consists

mainly of an “invisible” layer, which in practice is a surface contamination of the steel material.

The deposits formed by the second mechanism may consist of inactive elementary lead or various lead compounds, which in most cases have been found to be very thin. Deposits from unsupported lead have been observed on equipment, which has been in contact with produced water. The lead is found in the form of metallic lead or as chemical compounds such as lead sulphide (galena). It is expected that stable lead act as a carrier in the process. It has been observed that in the water phase unsupported lead is transported with brine. Lead sulphide is thought to form by a reaction with H₂S. The specific radioactivity of the lead or lead compounds is often quite high, in the order of kBq per gram. The mechanisms for transport and settling is not well understood, but are assumed to be as indicated in Fig.1.

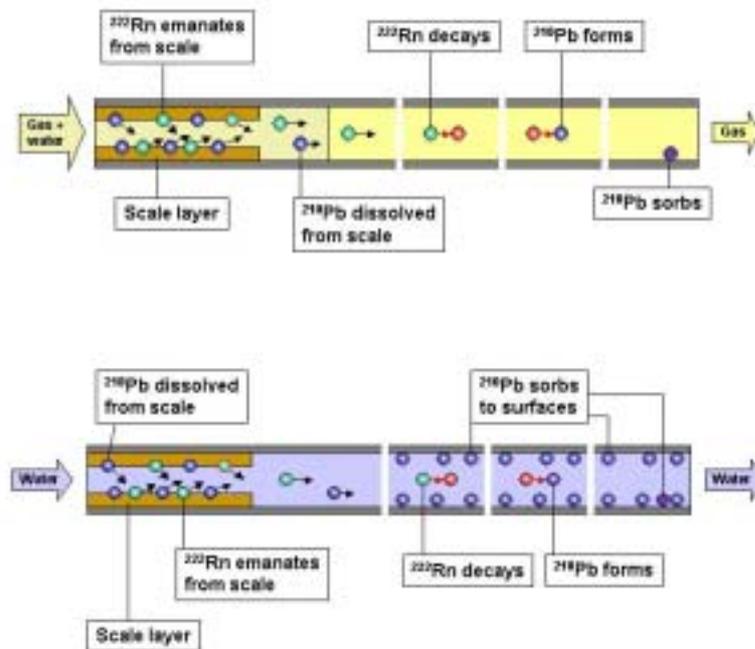


Fig.1. a. Generation ^{222}Rn from ^{226}Ra -containing scale and transport in a gas system. b. Simultaneous dissolution of ^{210}Pb from ^{226}Ra -containing scale and emanation of ^{222}Rn from the same scale and further transport in a water system

The data on the existence of lead scale is relatively scarce. Some information have however been gathered. Lead scale has however also been found at installations in the Norwegian sector (Fig.2). The lead scale probably constituted from lead sulphide transported in the water phase. It may be interesting to note that we find sulphate scale and lead scale in the near-well zone whereas equipment topside and in the upper part of the production string contains only lead scale. The specific activity of the lead deposit is typically 20 Bq/g in this case, and that is above the exemption limit.

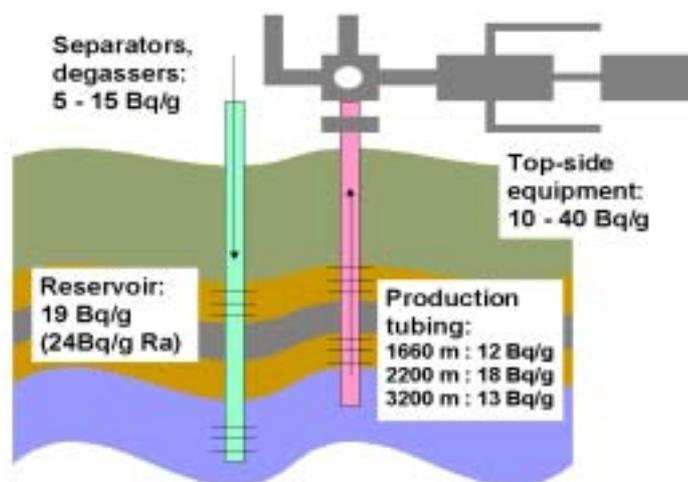


Fig. 2. Occurrence of ^{210}Pb -scale at an installation on the Norwegian shelf

Detection and classification

For measurement of ^{210}Pb one can take advantage of the weak low energy gamma ray emitted for laboratory measurements using high-resolution gamma spectrometry. The gamma radiation is however too weak to be detectable with hand-held instruments as for example Geiger-Müller counters. On-site measurements therefore must rely on detection of the beta radiation from decay of the daughter ^{210}Bi .

The aim of the measurements is usually to decide whether the scale is exempted or should be treated as radioactive material and subsequently radioactive waste. The exemption levels to be applied in the Norwegian sector have been put down by the Norwegian Radiation Protection Authority. A deposit should be regarded radioactive if the specific activity of any one of the nuclides ^{226}Ra , ^{228}Ra or ^{210}Pb exceeds 10 Bq/g.

The challenge for the industry is to determine on-site whether the component should be treated as radioactive or not. The criterion for a method to be used on-site is that it is simple to perform without long training. The equipment should be commercially available off-the-shelf. The method must of course have sufficient reliability to ensure that radioactive deposits are detected.

A method based on measurement of beta radiation from ^{210}Bi has been proposed. The equipment required for this is a standard beta-sensitive contamination monitor with a suitable probe. As such instruments only give the instrument specific reading counts per second, a calibration with scale standards must be undertaken. Such standards have been made available for the oil companies.

Consequences for the industry

Although not a big problem under ordinary operations, it may become one during service operations and decommissioning. The deposits of ^{210}Pb and progeny may be invisible, i.e. they exist as a mono- or a few- atomic layer on the steel surface with a relatively high surface activity. In such cases, necessary cleaning operations may not be implemented. This is clearly unfortunate in cases where the equipment is re-used in other industries (i.e. for instance in the water supply industry).

Radiation dose to personnel on- or offshore from ^{210}Pb deposits are expected to be negligible. There is, however, a certain risk for inhalation of airborne particles released during operation like cutting or welding of contaminated equipment. Intake can effectively be avoided using protective devices such as a dust mask and by a good working practise.

Small Doses of Radiation during Radiotherapy

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Abstract

Treatment of cancer by radiation is usually performed applying doses of ~2 Gy, given in 10 to 40 fractions. Consequently, the biological effects and their underlying molecular and genetic mechanisms have been regarded as distinct different from the effects and mechanisms relevant for low dose environmental exposure. Novel radiobiological insight has revealed that effects commonly observed at lower dose levels may be utilised in improving the therapeutic ratio in radiotherapy, i.e. the ratio between tumour and late toxicity of normal tissues and organs.¹

Introduction

Ionizing radiation is not only known to cause cancer, it has also been used for a century to treat cancer. To day, approximately 45% of all cancer patients are cured from their disease; 22% due to surgery, 12% by radiotherapy, an additional 6% by combined radiotherapy and surgery, and 5% by chemotherapy. Still, almost 20% of the patients die due to failure of local tumour control [1]. A report from the Swedish Council on Technology Assessment in Health Care [2], demonstrated that an increase in 5-year survival of 10 % could be achieved if established research results were implemented into clinical practice and routine. Although radiotherapy by no means is a novelty within cancer treatment strategies, this modality possesses still large potentials with respect to those patients who currently experience local failure.

The “Achilles-heel” of all current cancer treatment strategies is the late toxicity following treatment. Optimisation strategies in radiotherapy aims therefore at providing high local tumour control rates, and at the same time restrict the frequency and severity of late normal tissue effects to an acceptable level. Optimisation of radiotherapy follows in general two different strategies: (a) biological optimisation, i.e. dividing the total dose into smaller fraction sizes thereby allowing repair of radiation damage in normal tissue to a larger extent than in tumour tissue, and (b) physical optimisation, i.e. confine the high dose volume to that of the tumour tissue and microscopic disease, by applying numerous irradiation photon beams and a “cross fire” approach [1]. Traditionally, irradiation of tumour tissue has been

performed using daily fractions of 2 Gy, whilst normal tissue has received either approximately the same dose or 2-3 cGy. However, new treatment strategies aim at giving multiple fractions per day of 0.7-1.5 Gy to tumour tissue and 0.1-0.7 Gy to larger volumes of normal tissues and organs. The biological consequences of this altered treatment strategy with respect to late toxicity is, however, not obvious.

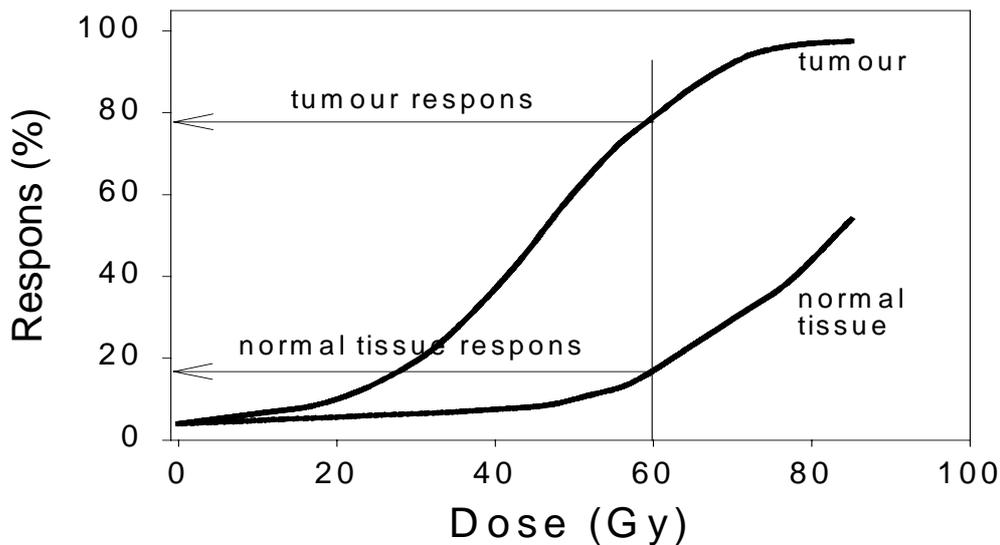


Fig. 1. Dose response relationships for tumors and normal tissue. The greater the distance between the two curves, the larger is the therapeutic ratio.

Radiation induced apoptosis:

The traditional explanation for cell kill following irradiation is based on indirect and direct damage of DNA, which during mitosis results in cell inactivation if not appropriately repaired. However, newer research in cell biology reveals that cellular inactivation may occur as a result of a diversity of processes. One of those which lately have gained particular interest in radiation biology, is the form of cell death named apoptosis. This process is regulated in numerous ways, e.g. by inhibition or blocking of protein synthesis. The apoptotic process is triggered at the G1 restriction point in the G1 phase of the cell cycle. Apoptosis may be induced by a number of stress factors, including radiation.

Apoptosis has been recognised as a major component in cell death in normal tissues, and as a crucial mechanism in the organogenesis of the foetus. However, apoptosis has not been seen in late reacting normal tissue. Moreover, tumour cells may undergo apoptosis, which

may represent a significant component of the treatment response. The amount of mitotic cell kill due to irradiation has been suggested to be linear-quadratic dependent of the dose, D:

$$SF = e^{-(\alpha \cdot D + \beta \cdot D^2)} \text{ (eq. 1)}$$

where α and β are radiosensitivity parameters and SF is the cell surviving fraction. Equation (2) is often referred to as the LQ-model.

This model does not take into account different modes of cell inactivation, and does not differ between the mitotic component and the apoptotic component of the cell inactivation following irradiation. Following the modelling work of Ling and co-workers [3], a new model for cell survival following fractionated irradiation was established [4]:

$$SF_n = \left[F_a \cdot e^{-\xi \cdot D} + (1 - F_a) \right]^n \cdot e^{-(\alpha \cdot D + \beta \cdot D)^2 \cdot n} \text{ (2)}$$

Here, SF_n is the surviving fraction after n treatment fractions, ξ is the sensitivity with respect to radiation induced apoptosis, and F_a is the maximum apoptotic fraction that possibly can be induced by radiation.

The ratio between the surviving fraction of normal tissue cells and tumour cells may be denoted the “biological effect ratio” BR, and may represent an indicator of the local tumour control vs. normal tissue toxicity following irradiation. BR may be calculated based on published data for tumour tissue, both with respect to mitotic as well as apoptotic cell kill. As apoptosis has not been reported for late sequela, the only contribution to normal cell inactivation resulting in late toxicity, arises from calculations of mitotic cell kill. Figure 2 shows that the biological effect ratio increases as the dose per fraction decreases, and increases with increasing maximum apoptotic component. This indicate that when the treatment is divided into a larger number of fractions, each of smaller dose, relatively fewer tumour cells will undergo mitotic cell inactivation and more will proceed through the cell cycle entering G1 where p53 at the G1 restriction point may trigger apoptosis of the cell.

It has been documented through numerous clinical studies that an improved therapeutic ratio (biological effect ratio between normal tissue and tumour tissue) is achieved as the dose per fraction is reduced. However, the mechanism behind this effect has previously not been fully understood. The recent results indicate that apoptosis may represent an important contribution to this mechanism. Moreover, new treatment strategies may emphasise on stimulating apoptosis in combination with fractionated radiotherapy.

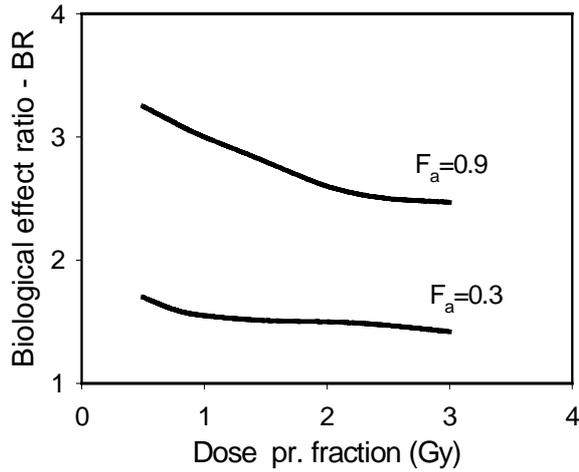


Figure 2. Calculated ratio between normal tissue and tumour cell survival, calculated for a fractionated radiotherapy scheme using α/β of 3 for normal tissue, 10 for tumour; $\xi=0.3$ for tumour tissue and 0 for normal cells (4).

Radiation hypersensitivity:

Studies by Mike Joiner [5] and others have shown that cell survival, predicted by the LQ formalism (eq. 2), is vastly overestimated compared to experimental data for dose levels between 0.3-0.7 Gy. This effect, which has been named radiation hypersensitivity, has also recently been

observed in a clinical study conducted by Turrenson and Joiner [6], where the incidence of skin erythema was investigated with respect to variable dose per fraction.

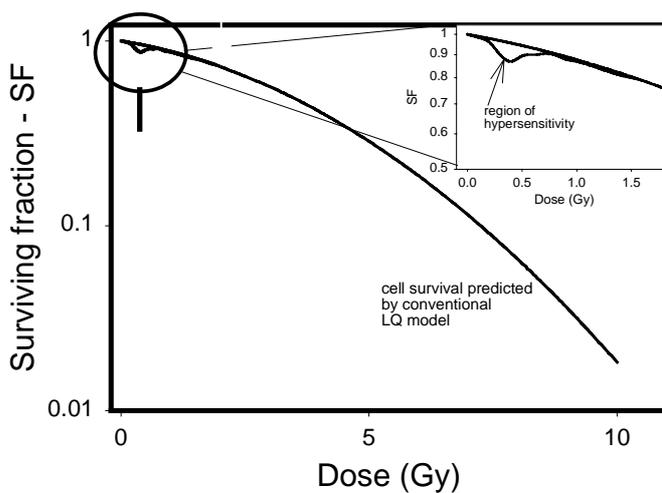


Fig. 3. Illustration of cell survival curves calculated using the conventional LQ formalism, and the hypersensitivity model published by Joiner et al. [6]

They conclude that the tolerance was reduced at doses per fraction lower than 2 Gy, and higher than 3 Gy. Also, Joiner et al has proposed a modification of the conventional LQ-formalism (eq. 1) to account for the radiation hypersensitivity [6], named the hypersensitivity model. The hypersensitivity model predicts the actual cell survival with greater precision, especially in the low dose region than the conventional LQ model.

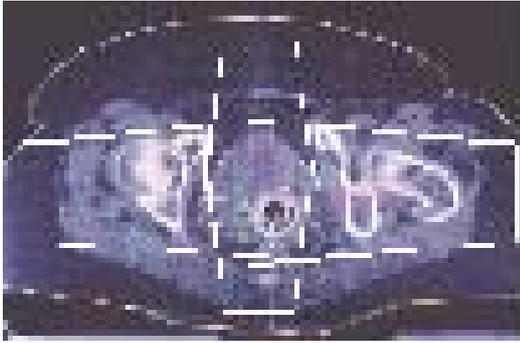


Fig. 4. CT image of the pelvic, showing a 4 beam irradiation technique for ca. cervix. Areas within the beams, but not included in the “cross fire ” -region will receive 0.3-0.7 Gy. Photon beam borders are marked with white lines.

The observation of radiation hypersensitivity in low dose regions may have significant clinical impact, not only with respect to erythema of the skin, but also with respect to soft tissues. Modern therapy techniques apply multiple photon beams, often 4-10 beams, directed towards the tumour volume. The immediate consequence is that most soft tissue areas included in the irradiated areas, but not included in the “cross fire”-area (i.e. the high dose irradiated areas), receives doses of 0.3-0.7 Gy. This dose level corresponds to the region of radiation hypersensitivity, and may result in increased frequency of normal tissue late toxicity compared to what is predicted by conventional LQ-formalism. Figure 5 show the biological effect, converted into total treatment dose, given as 2Gy-fractions (i.e. standard fractionated irradiation), taking into account the radiation hypersensitivity using the hypersensitivity model [5]. The figure shows an increased biological effect of doses per fraction less than 0.6 Gy. In current treatment strategies, normal tissues and organs are usually spared by distributing the dose to a larger volume and to dose levels of 0.3-0.7 Gy. Consequently, radiation hypersensitivity may cause a substantially larger biological effect in normal tissue than expected. Physical optimisation the way it’s currently developing, may therefore not be in accordance with the criteria of biological optimisation.

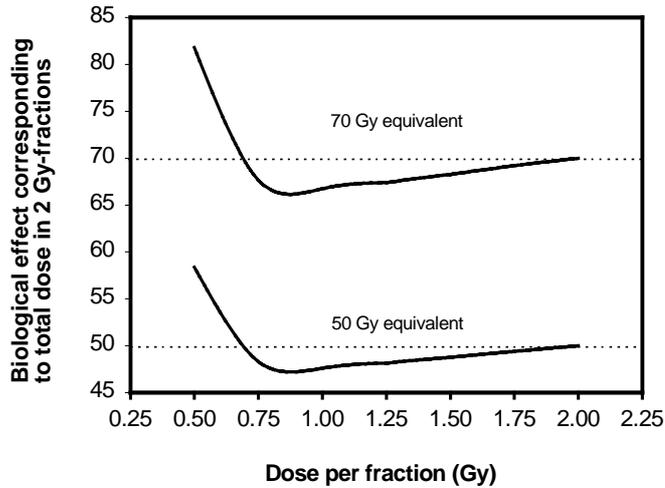


Fig. 5. The biological effect of a fractionated regime of 50 and 70 Gy, taking into account radiation hypersensitivity, given in 2Gy- equivalent total dose.

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