23

Rapid #: -4319491

Ariel
IP: 129.252.80.49

ARC 9-13

Status	Rapid Code	Branch Name	Start Date
Pending	UUM	Marriott Library	4/5/2011 3:08:30 PM

CALL #: **RA1231.R2 J6**

LOCATION: **UUM :: Marriott Library :: ARC Journals ML: ARC available by request**

TYPE:	Article CC:CCG
JOURNAL TITLE:	Journal of radiological protection
USER JOURNAL TITLE:	Journal of Radiological Protection (Formerly : Journal of the Society for Radiological Protection)
UUM CATALOG TITLE:	Journal of radiological protection.
ARTICLE TITLE:	Human exposure to high natural background radiation: what can it teach us about radiation risks?
ARTICLE AUTHOR:	Hendry, J. H., Simon, S. L., Wojcik, A., Sohrabi,
VOLUME:	29
ISSUE:	2A
MONTH:	
YEAR:	2009
PAGES:	A29-A42-
ISSN:	0952-4746
OCLC #:	UUM OCLC #: 18265885
CROSS REFERENCE ID:	[TN:925158][ODYSSEY:129.252.106.237/COLUM]
VERIFIED:	

BORROWER: **SUC :: Main Library**

PATRON: **Tim Mousseau**

PATRON ID:	mousseau
PATRON ADDRESS:	
PATRON PHONE:	
PATRON FAX:	
PATRON E-MAIL:	
PATRON DEPT:	
PATRON STATUS:	
PATRON NOTES:	

RAPID ILL

System Date/Time: 4/6/2011 8:42:40 AM MST

IOP PUBLISHING JOURNAL OF RADIOLOGICAL PROTECTION

J. Radiol. Prot. **29** (2009) A29–A42 doi:10.1088/0952-4746/29/2A/S03

Human exposure to high natural background radiation: what can it teach us about radiation risks?

Jolyon H Hendry[1,9], Steven L Simon[2], Andrzej Wojcik[3,4,10], Mehdi Sohrabi[1], Werner Burkart[1], Elisabeth Cardis[5], Dominique Laurier[6], Margot Tirmarche[6] and Isamu Hayata[7,8]

[1] Department of Nuclear Sciences and Applications, International Atomic Energy Agency, Vienna, Austria
[2] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
[3] Institute of Nuclear Chemistry and Technology, Warsaw, Poland
[4] Institute of Biology, Swietokrzyska Academy, Kielce, Poland
[5] Centre for Research in Environmental Epidemiology (CREAL), Municipal Institute of Medical Research (IMIM-Hospital del Mar) and CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain
[6] Radiobiology and Epidemiology Department, Radiological and Human Health Division, Institute for Radiological Protection and Nuclear Safety, Fontenay-aux-Roses, France
[7] National Institute of Radiological Sciences, Chiba, Japan
[8] Central Research Institute of Electric Power Industry, Tokyo, Japan

E-mail: jhendry2002uk@yahoo.com

Received 29 September 2008, in final form 5 January 2009, accepted for publication 12 January 2009
Published 19 May 2009
Online at stacks.iop.org/JRP/29/A29

Abstract

Natural radiation is the major source of human exposure to ionising radiation, and its largest contributing component to effective dose arises from inhalation of ^{222}Rn and its radioactive progeny. However, despite extensive knowledge of radiation risks gained through epidemiologic investigations and mechanistic considerations, the health effects of chronic low-level radiation exposure are still poorly understood. The present paper reviews the possible contribution of studies of populations living in high natural background radiation (HNBR) areas (Guarapari, Brazil; Kerala, India; Ramsar, Iran; Yangjiang, China), including radon-prone areas, to low dose risk estimation.

Much of the direct information about risk related to HNBR comes from case–control studies of radon and lung cancer, which provide convincing evidence of an association between long-term protracted radiation exposures in the general population and disease incidence. The success of these studies is mainly due to the careful organ dose reconstruction (with relatively high doses to the lung), and to the fact that large-scale collaborative studies have

[9] Address for correspondence: Adlington, Macclesfield, Cheshire SK10 4JU, UK.
[10] Present address: GMT Department, Stockholm University, Sweden.

0952-4746/09/2A0029+14$30.00

been conducted to maximise the statistical power and to ensure the systematic collection of information on potential confounding factors. In contrast, studies in other (non-radon) HNBR areas have provided little information, relying mainly on ecological designs and very rough effective dose categorisations. Recent steps taken in China and India to establish cohorts for follow-up and to conduct nested case–control studies may provide useful information about risks in the future, provided that careful organ dose reconstruction is possible and information is collected on potential confounding factors.

1. Introduction

Understanding the health impacts of low-level chronic public exposure is critical to providing a rational basis for regulating radiation exposure in today's society. There are several scenarios of such exposures, from nuclear activities, e.g. Techa riverside residents in the 1950s, nuclear accidents, e.g. post Chernobyl, and radioactive contamination in buildings, e.g. in Taiwan. The question continues to be asked whether there is evidence of risk or expectation of detriment based on projections from other sources of evidence. There are few opportunities to conduct relevant studies that can successfully quantify such risks directly.

Studies of the health of populations living in areas of high levels of natural radiation are a potential source of information on the effects of chronic low dose-rate exposures. This paper aims to discuss populations which, if studied, may provide important information, to review existing studies, and to discuss criteria for future studies so that they are informative.

2. Sources of high natural background radiation

Natural background radiation that originates from the terrestrial environment varies tremendously worldwide, and usually within countries as well. The primary radioactive elements in the Earth's crust that lead to human exposure are potassium, uranium, thorium, and their radioactive decay products (e.g., radium, radon, etc). There are many reviews of natural radioactivity; see e.g. [1].

A high natural background radiation (HNBR) area is defined as an area or a complex of dwellings where the sum of cosmic radiation and natural radioactivity in soil, indoor and outdoor air, water, food, etc leads to chronic exposure situations from external and internal exposures that result in an *annual effective dose* to the public above a defined level. The annual effective dose rate has been classified into four levels: low, meaning = 5 mSv y^{-1} (or about twice the global average of 2.4 mSv y^{-1} reported by UNSCEAR); medium (5–20 mSv y^{-1}); high (20–50 mSv y^{-1}); and very high (>50 mSv y^{-1}) [2, 3]. This classification system also considered the dose limits of ICRP 60 [4] and the International Basic Safety Standards [5]. Other major reports have also classified dose levels, but in terms of total doses; for example, the BEIR VII [6] report defined low doses as those in the range of near 0 up to about 100 mGy (cumulative doses) of low-linear-energy-transfer radiation, while medium-level and high-level doses were considered beyond the ranges of interest in environmental studies. The French Academy of Sciences report quantified low total doses as <100 mSv and very low doses as <10 mSv [7]. Regarding the definition of a high radon area, there has been no standard definition given in the literature, though some existing or proposed criteria were reviewed by Sohrabi [2]. In that context, the definition of an HNBR area, of above 20 mSv y^{-1} (the same as the occupational dose limit recommended by ICRP), also covers a potentially high radon area.

The most studied areas with high levels of terrestrial radiation are in Brazil, China, India, and Iran, while radon-prone areas have been studied in many countries.

Brazil. The main areas studied are the Poços de Caldas, Araxà, and Tapira, comprising the zone of volcanic alkaline intrusive in the Minas Gerais State, as well as Guarapari, located in the Espirito Santo State on the Atlantic Coast [8]. Six thousand persons reside in the HBNR area in Poços de Caldas, 1300 in Araxà, and 12 000 in Guarapari. The level of exposure received since the years of the earliest publications has changed significantly due to urbanisation and movement of the population away from the high background area. The annual effective doses from external and internal exposures are now less than about 7 mSv. Recent assessments have been performed at Poços de Caldas [9] and Guarapari [10]. There it was found that the radiation level in Guarapari can be considered as normal (near average global levels) except at hot spots on the beaches and in the fishing village of Meaipe [10]. Also, at Poços de Caldas, it was reported that only rural areas could be considered as HNBR areas, and the radiation level in urban areas can be considered as normal [11].

China. The HNBR area of Yangjiang County (Guangdong province) in the south of China consists of two regions (Dong-anling and Tongyou) separated by a short distance. The HNBR area covers a total area of about 540 km^2 [12]. More than 125 000 people, primarily farmers, live in the two regions. Residents whose families have lived in those areas for six or more generations comprise 90% of the population. In this region, fine particles of monazite are washed down the mountains by rain to the surrounding basin regions, giving rise to the HNBR areas. The level of natural radiation is high due to radionuclides such as ^{232}Th and ^{238}U in the surface soil and in the building materials of houses [13]. The average annual effective dose was reported to be 6.4 mSv, with an external dose of 1–3 mSv (average 2.1 mSv) and an internal dose of 4.3 mSv, about three times higher than that of control areas.

India. Kerala is a densely populated, monazite-bearing coastal region in southwest India. Radiation exposure in these areas is mainly due to the presence of thorium and its decay products in the surface soil. Its 360 000 inhabitants, who generally have low migration rates, receive annually, on average, external whole-body doses of about 4.5 mGy from gamma-rays plus an internal dose of 2.4 mSv (effective dose) from exposure to radon. The typical high end of the dose range is about 10 mGy from gamma-rays plus 6 mSv from radon, though a considerable range of 1 to about 45 mSv y^{-1} has also been reported [1, 14, 15].

Iran. Ramsar is a northern coastal city in Iran with over 50 sulfurous hot springs that contain enhanced ^{226}Ra concentrations. This water has ^{226}Ra concentrations of up to 146 kBq m^{-3} and it flows into the surrounding areas, adding more radioactive residues to the existing radioactivity in the environment. Ramsar has a population of 60–70 000, though only about 1000 people reside in the HNBR areas. The annual effective doses received by the inhabitants from external exposures (indoors and outdoors) range between 0.7 and 131 mSv with a mean of 6 mSv [16], and the internal dose due to ^{222}Rn ranges from about 2.5 to 72 mSv [17].

Radon-prone areas. Measurement programmes of indoor radon concentrations have been conducted in many countries [18–20]. According to ICRP [21], one year of breathing air with a concentration of 300 Bq m^{-3} corresponds to an effective dose of 5 mSv. In Europe, the percentage of houses above 400 Bq m^{-3} (i.e. above about 7 mSv effective dose) varies from 0 to more than 10% depending on the country [20].

3. Methodological considerations for studies of health effects associated with HNBR areas

In order for studies of populations exposed to HNBR to provide information on the effects of chronic low dose-rate exposures to ionising radiation, they must meet a number of

important methodological requirements, including appropriate study design and sufficient statistical power, and they must have available individual estimates of doses to specific organs from internal and external exposures, and individual information on known and possible risk factors for the diseases of interest. For most studies of HNBR to date, with the exception of studies of lung cancer in relation to radon, these requirements have not been met.

A requirement that is often underestimated is the population size. The approximate size of the population required to detect differences in excess cancers with 80% statistical power can be calculated. These data can be roughly interpreted to estimate sample size requirements for a study of HNBR areas using particular annual doses. For example, if a mean internal plus external effective dose of 6 mSv y^{-1} is assumed, as might be received in the HNBR areas of China or Iran, and it is agreed to study the population having reached 10 years of age (or having received 60 mSv), lifetime surveillance of about 56 000 persons would be required to reliably observe about 45 excess cancer cases (assuming an incidence according to the linear-no-threshold (LNT) model) among nearly 17 000 cancers likely to occur in a similar non-exposed population. While identifying a sample of 56 000 persons is achievable, the difficulty in conducting the follow-up of that many people during the remaining 60 years or more of life would be great.

Other health endpoints may be more useful indicators of radiation induced risk than total cancers. For that reason, the NRC [22] estimated the numbers of exposed persons necessary to detect an excess mortality from leukaemia and respiratory cancer. Assuming a dose to bone marrow approximately equivalent to effective dose (a reasonable assumption at ~0.5 MeV, i.e., at γ-ray energies typical of HNBR areas), estimations of sample sizes required to detect excess leukaemia can be derived. For example, if a mean external effective dose of 2–6 mSv y^{-1} is assumed, as might be received in the HNBR areas of China, Iran, India, or limited areas in Brazil, and it is agreed to study the population having reached 10 years of age (or having received 20–60 mGy), lifetime surveillance of 0.13–1.2 million persons could achieve 80% power. Similar considerations apply for radon and lung cancer. While these figures are only for illustration, it is clear that the sample size requirements for specific cancer sites are more stringent than for all cancers together.

The issue of statistical power also applies to studies with biological endpoints other than cancer, e.g. the power of dicentric yields, often used as a biological indicator of the absorbed dose [23, 24]. A large collaborative six-laboratory study showed that an acute dose of 20 mGy *in vitro* could be detected using 30 000 scored cells. The background frequency of dicentrics is around 1 in 1000 cells, and the induction rate per 10 mGy is about 3 in 10 000 cells [23]. When the number of analysed cells is around 1000, the detection limit of radiation exposure in a healthy individual is about 100 mGy due to the uncertainty in the background frequency of dicentrics [24]. The average annual effective dose from natural background radiation in the world is about 2.4 mSv [25] and, hence, about 160 mSv is accumulated over a 65-year life [26]. Thus, it is possible to detect the effect of an elevated dose level of natural radiation providing that a reasonably large number (at least 1000) of cells per individual and many individuals [27] are analysed.

4. Review of health and biological effects

A number of epidemiological studies have been conducted during the last 25 years to evaluate the health effects of exposure to elevated natural background radiation. These include descriptive studies in HNBR areas of Brazil, India, Iran, and China, as well as analytical studies, mainly case–control studies of lung cancer risk associated with indoor radon exposure. In addition, cytogenetic studies, focusing on chromosomal aberrations in peripheral blood

lymphocytes (PBLs); have been performed in HNBR areas. Reported studies are summarised briefly below.

Brazil. No formal epidemiological study has been conducted in HNBR areas of Brazil. A recent descriptive study has, however, compared mortality rates over the period 1991–2000 in the regions of Poços de Caldas (population 120 000) and Araxà (90 000), with those in the entire Minas Gerais State. A significantly elevated standardised mortality ratio (SMR) was found for cancers in Poços de Caldas and for non-cancer mortality in both regions [11]. No information is available on mortality rates in the much smaller HBNR areas in these regions.

13 242 lymphocytes from 202 persons in Guarapari and 9001 lymphocytes from 147 persons in control areas were analysed for the presence of chromosomal aberrations. However, the culture period of lymphocytes in this study was too long (72 h) for analysing aberrations specific to radiation [28].

China. Tao *et al* [29] studied cancer mortality between 1979 and 1995 in the HNBR area of Yangjiang. They followed over 100 000 subjects for 19 years and observed 557 cancer deaths. The average annual effective dose (including internal dose) was reported to be 6.4 mSv. The population was subdivided into three cumulative dose groups based on annual dose rate in the area of their residence, and the risk was compared with that for those living in control areas. No increased cancer mortality risk was found to be associated with living in the HNBR areas when all cancer deaths were included (without restriction due to questionable diagnoses). Restricting their analysis to only cancer deaths diagnosed pathologically, the relative risk (RR) increased from 0.71 (95% confidence interval (CI): 0.51–0.99) to 0.92 (95% CI 0.79–1.08).

A more recent analysis for the Yangjiang area was performed based on an extended follow-up of the cohort over 20 years [30]. Mortality rates from cancer were not observed to differ between HNBR areas and control areas in China over 20 years. There was also no association observed between cancer mortality and external radiation dose, though the dose–response analyses were based on three relatively similar low dose groups (<1.98, 1.98–2.24, >2.24–3.1 mSv y^{-1}) that do not discriminate between subjects with doses of very different magnitude. A significant effect was seen, however, between HNBR areas and control areas with respect to non-cancer mortality, including cerebro-vascular diseases, tuberculosis, viral infections, and diseases of the digestive system (in particular chronic liver disease) [30]. In these studies, information on other risk factors for these diseases (including smoking, hepatitis B virus infection, alcohol consumption, consumption of some food stuffs) was not taken into account, and therefore no inferences on radiation effects other than cancer can be drawn. The study of Zhou *et al* [30] relied on the follow-up of the mortality of populations in time, and is clearly of cohort design. Nevertheless, it is emphasised that the analysis consists only in a comparison of rates between the HNBR and the control areas, which is closer to an ecological design.

The rate of hereditary and congenital diseases has also been studied in China, in a population of 13 000 children less than 12 years old who were born in the HNBR areas. A total of 31 different diseases were considered. Overall, no difference in rates was observed between those born in HNBR and control areas. Considering Down's syndrome, a higher frequency was observed in the HNBR area compared to the control area, but this result was based on a very low number of cases [31]. The observation could be due to a particularly low rate of Down's syndrome in the control area, because the rate in the HNBR area was not higher than the UNSCEAR estimate of the spontaneous rate of occurrence. Another explanation could be some confounding by mothers' ages, a very important determinant of Down's syndrome risk, which were not controlled for.

More recently, a nested case–control study was launched to study lung cancer risk in the HNBR area in China. The study is relatively small, with 63 cases and 126 controls.

Information about smoking was collected for each individual. Indoor radon concentration was measured using passive detectors. A significant effect of smoking was found, but no significant association could be demonstrated with external dose or with radon exposure [29].

Chromosomal aberrations in the PBLs of people living in the region of Yangjiang in South China have been analysed. Unstable-type aberrations (dicentrics and rings) were analysed in the PBLs of 22 people of different ages with accumulated lifetime doses in the range 30–360 mGy [32]. The group of controls included 17 subjects of a similar age distribution who received lifetime doses of 6–60 mGy. Mean frequencies of 1.45 and 0.76 aberrations were observed in the PBLs of inhabitants of an HNBR area and a control area, respectively. The difference in the frequencies of dicentrics in adults was statistically significant, but not for those in children. Stable-type chromosomal aberrations were analysed by chromosome painting in another group of subjects: 30 from HNBR and 27 from control areas [33, 34]. In subjects from both areas, the frequencies of translocations were much higher than those of dicentrics. However, no statistically significant difference was observed between the results in HNBR and control areas. The contribution of increased exposure to natural radiation on the induction rate of translocations did not have a significant effect compared to the contribution of other mutagenic factors such as chemicals and/or metabolic factors [35]. It was found that the HNBR played a less significant part than smoking in increasing the induction rate of translocations.

India. In the 1970s, a study concluded there was an elevated frequency of Down's syndrome in Kerala [36]. That study, however, was based only on a crude assessment of prevalence data (i.e., the number of cases in a given population). An incidence study of congenital malformations among 42 000 births in Kerala between 1995 and 1999 has been conducted. Several potential confounding factors were considered, including the bias introduced by twins, consanguinity, mother's age, and gender. In these later studies, no association between Down's syndrome and radiation dose was observed, but the finding relied on only 25 observed cases [37].

Since 1990, a cancer registry has been implemented in the Kerala region. Previous ecological studies indicated geographical variations of cancer incidence within Karunagappally, but with no relation with the geographic distribution of exposures [38]. A more ecological analysis, based on more than 3600 cancers recorded over the period 1990–2001, showed no association between cancer incidence and mean external radiation dose level [39]. Although a large cohort of over 380 000 people has been identified and information collected on external dose and lifestyle factors, no analytical study has been published to date.

A study of lung cancer risk has been conducted, based on a case–control design. The study included 205 cases and 615 controls. Information about smoking was collected for each individual. The external dose was derived from measured dose rates at the place of residence. No significant association was observed in relationship to the external dose, although an odds ratio of 2.3 (95%CI = 0.9–5.7) was observed for the small number of subjects living at a location where the external dose was greater than 10 mGy y^{-1} [40]. No information is available on the levels of internal dose to the lung and to other organs in studies in India. As the dose to the lung is likely to be much higher than the dose from external exposures, it is difficult to interpret the results of studies to date.

Between 1986 and 2000, chromosomal aberrations were analysed in the PBLs of 14 217 newborns in the Kerala region whose mothers were exposed to annual whole-body absorbed doses of 1.5 mGy or more and in the PBLs of 5719 newborns whose mothers were exposed to annual doses less than 1.5 mGy [41, 15]. The analysis included numerical and structural (i.e. stable and unstable) aberrations. A total of nearly 1 million metaphases was scored. No correlation was found between the background radiation dose and the frequency of chromosomal abnormalities. The reason for the null results could be that the time of exposure

of the newborns (<1 y) was not long enough to increase the dicentric yields to a detectable level. Cheriyan *et al* [41] also examined 32 700 cells from 185 Kerala residents exposed to 2.8–6.3 mGy y^{-1} and in 20 385 cells from 125 persons living in an area with an exposure level of about 0.90 mGy y^{-1}. Furthermore, 11 468 cells were examined from 62 workers in a monazite processing plant who had been exposed to doses from 1.0 to >20 mGy. The pooled frequencies of dicentrics and rings per 1000 cells were 1.3 ± 0.2 in the HNBR residents, 0.7 ± 0.2 in the control area residents, and 2.2 ± 0.4 in the workers, and hence significantly different values for the three groups.

A finding of note is that family pedigrees living in the HNBR area were found to have an increased level of germ-line point mutations between mothers and their offspring [42]. This implied that the radioactive conditions accelerated the mutations that have been evolutionary hotspots for more than 60 000 years.

Iran. Mortality rates among residents in the HNBR area (about 3000 persons in the highest dose level areas, 7000 in the lower dose level area) were compared with national rates over the period 1998–2001. The SMR for cancer was increased (1.3 and 1.2 respectively in high and low radiation areas, statistical significance not quoted), but only in women [43]. Due to the small size of the population living in the area and to the very short study period (4 years), these results rely on very few cancers deaths (41 in total among men and women). Only one death from cancer was in men in the high dose level areas, compared with six in women, suggesting a possible under-ascertainment of deaths [43]. Considerable investment in a local cancer registry would be needed to draw any conclusions.

In preliminary studies, no significant differences were found between aberrations in lymphocytes of 21 subjects from the HNBR and 14 subjects from normal background areas in Iran [44, 45]. In a later more detailed study, chromosomal aberrations were analysed in the lymphocytes of 50 long-term inhabitants of Ramsar (with annual effective doses between 1.6 and 42 mSv) [46]. The frequencies of both unstable and stable chromosomal aberrations were compared with those observed in the lymphocytes from 30 age-matched inhabitants of a nearby control area where the mean annual effective dose was 2.3 ± 0.1 mSv. In that analysis, significantly increased frequencies of both aberration types were observed in the lymphocytes of Ramsar inhabitants as compared to control areas. The unstable aberrations were mostly breaks but the authors found no dicentrics in 18 200 cells.

Indoor radon. Both ecological studies and case–control studies have been conducted to analyse the risk of lung cancer in relation to indoor radon exposure. About 20 ecological studies have been published around the world since the 1980s; see e.g. [47–50]. Results from these studies were inconsistent, and these inconsistencies are considered to be due mainly to the difficulty in adequately adjusting for the confounding effects of smoking on a geographic level, as well as to the large variation of radon concentration inside geographical units [51]. The BEIR VI committee concluded that ecologic studies of indoor radon exposure and lung cancer were 'essentially non-informative and shed little light on the association of indoor radon-progeny exposure and lung cancer' [50].

In the past decades, several well-conducted epidemiologic studies have investigated the risk of lung cancer in relation to indoor radon exposure via case–control studies where details of individual residential histories and smoking habits have been gathered. Radon concentrations in indoor air were evaluated by various methods, but in all the more recent studies, radon concentrations were assessed in the subjects' homes by long-term (6 months or 1 year) measurements with alpha track detectors. Such measurements allow for the calculation of a time-weighted average concentration that accounts for seasonal and other short-term variations which can be misleading. Some of the studies suggested that residential radon is a risk factor

for lung cancer, with risk estimates consistent with those derived from studies of miners. In other studies, no clear effect was observed. In reviewing the findings from indoor case–control studies, the studies with more complete and accurate radon measurement data have indicated a statistically significant association between indoor radon exposure and lung cancer. The inability of some studies to detect an association is likely to be due to poor assessment of past radon exposure [52, 53]. Despite the uncertainties that affect the results of the case–control studies, the estimated risks appear consistent as a group.

Recently, the results of coordinated research programmes in Europe and in North America have been published [54–56]. In Europe, a collaborative approach gathered individual information from 13 case–control studies conducted in nine different countries. A total of more than 7000 cases and 14 000 controls were included in the analysis, providing sufficient statistical power. In addition, the European collaboration also provided the basis for standardising data collection efforts in the different studies through the discussion of study design, the development of common questionnaires, and campaigns of comparison of indoor radon measurements [57]. A joint analysis led to an RR of 1.08 per 100 Bq m^{-3} (95% CI: 1.03–1.16) [58]. In parallel, a North American project gathered data from seven case–control studies in Canada and in the USA [55]. That joint analysis included more than 3600 cases and about 5000 controls. The estimated RR per 100 Bq m^{-3} was 1.11 (95% CI: 1.00–1.28).

Detailed dosimetric calculations of inhalation of radon progeny show that organs other than lung received some, albeit much lower, radiation dose [59]. Nevertheless, at present, no effect other than lung cancer can be ascribed to radon exposure [50]. For leukaemia, numerous studies have been performed, but a positive association suggested by ecological studies has not been confirmed by studies based on individual data [60, 61].

The effect of domestic radon on the level of chromosomal aberrations in PBLs has been analysed by several investigators, even though effects are not expected to be seen because the dose is delivered primarily to lung tissue. The results have been contradictory, as might be anticipated. For example, enhanced frequencies of unstable aberrations were observed in the PBLs of children in a school with indoor radon concentration up to 7000 Bq m^{-3} [62] and in the PBLs of cave tour guides [63]. Oestreicher *et al* [64] analysed unstable-type and stable-type aberrations in the PBLs of 61 people from China living in houses with radon concentrations between 80 and 13 000 Bq m^{-3}. Enhanced frequencies of both aberration types were observed. Bauchinger *et al* [65] also studied unstable-type and stable-type aberrations in the PBLs of 25 individuals from Bavaria who lived in nine houses with radon concentrations between 210 and 3000 Bq m^{-3}. Compared to 32 controls, statistically elevated frequencies of dicentrics were detected, and the frequencies of translocations tended to be higher. The authors contended that the negative result was due to a relatively high level of background translocations in the PBLs of the control individuals that masked the effect of radon exposure. A very thorough study with precisely matched donors was performed by Lindholm *et al* [66], who analysed the PBLs of 28 Finnish donors from each of three exposure groups: homes with radon concentrations (1) below 100 Bq m^{-3}, (2) between 200 and 400 (mean 293) Bq m^{-3}, and (3) over 800 (mean 1737) Bq m^{-3}. Only donors who lived in the houses for at least 10 years were chosen for analysis. The same frequencies of unstable-type and stable-type aberrations were observed in the PBLs of donors from all groups. No influence of domestic radon on the frequencies of chromosomal aberrations was observed in two other studies [67, 68].

5. Discussion

Health effects. Large-scale epidemiological studies have been conducted to analyse the frequency of health effects in HNBR areas, essentially in India and in China. Most of these

studies were of ecological design. These studies mainly considered the risk of cancer, globally or for specific cancer sites, on the basis of mortality data or of incidence data. Some studies also considered the risks of non-cancer diseases or of congenital malformation. Overall, these studies demonstrated no increased risks in the HNBR areas compared to control/reference populations. The recent study in Yangjiang, China, showed a significant excess of non-cancer mortality, including cerebro-vascular diseases, tuberculosis, viral infections, and diseases of the digestive system, but these results should be considered with caution due to uncontrolled confounding factors. Another study in China observed a higher frequency of Down's syndrome in the HNBR area compared to the control area, but this result was based on a limited number of cases, and again some major confounding factors were not controlled for.

Regarding radon, the association between radon exposure and lung cancer risks was long ago demonstrated from miner cohort studies [50]. Nevertheless, the risk of exposure to radon indoors in the domestic environment has long been questioned. About 20 ecological studies have been performed since the 1980s, but due to methodological limitations these studies proved unable to answer the question. Indoor radon case–control studies have been conducted in many countries since the 1990s. Most of these studies demonstrated no association, due to low statistical power, insufficient control of confounding factors, or poor assessment of past radon exposure. Coordinated research programmes launched in Europe and in North America enabled an increase in the statistical power of these studies and provided the basis for standardising data collection efforts. These international efforts have confirmed the existence of a significant risk of lung cancer associated to indoor radon exposure. Furthermore, the order of magnitude of these estimations agrees well with extrapolations from studies on miners.

Biological effects. Reported frequencies of chromosome aberrations have varied depending on the specific study and the location. For example, increased frequencies of dicentrics were detected from residents of HNBR areas in China and India. In Iran, only chromatid-type aberrations (not specific for radiation) were found to be enhanced. However, the frequencies of translocations from residents in HNBR areas in China were generally greater than those of dicentrics and exceeded the expected values estimated from a physical estimate of accumulated dose. There is a minimal level of HNBR dose rate below which the effect of radiation becomes undetectable due to the large individual variation of the effect of non-radiation mutagens such as chemicals and endogenous metabolic factors such as reactive oxygen species [69, 26, 70].

The data on the influence of domestic radon on the level of cytogenetic damage are conflicting. Interestingly, no enhanced levels of dicentrics or translocations have been observed in the PBLs of uranium miners who are generally exposed to radon concentrations that considerably exceed those found in households [71, 72].

Limitations of HNBR studies. Studies of human exposure to HNBR pose many problems, and several researchers have generally concluded that such studies are unlikely to provide definitive answers, even under the best of circumstances [73]. The limitations of studies of exposure to HNBR are several; for example, many countries that contain HNBR areas do not have well-documented health statistics, in particular, organ-specific cancer rates.

The effects of low-level exposures are likely to be small, according to our present understanding. It is, therefore, important to consider the attributable risk that might be expected if current risk estimates derived from A-bomb survivors and other high dose populations are applicable to chronic exposure. Based on dose distributions, about a 3% increase in all cancer risk in the HNBR areas in China (i.e., about 25 extra cancer deaths out of 855) and a 1–1.5% increase in genetic risk in India (where studies of such endpoints are foreseen) would be expected. The populations living in HNBR areas in Brazil and Iran are much smaller than those in HNBR areas in China or India; hence, even with dose levels higher in the former areas,

the number of cases would be small. The small expected increases underscore the difficulties in making observations that reach statistical significance.

A large part of the difficulty facing new health effects studies of HNBR areas is the absence of well-documented cancer rates. Finding satisfactory groups that may be considered as low exposed with respect to those that are high exposed remains a significant challenge. In most situations the expected difference linked to mean exposure of each group is a 'weak' indicator, because these populations may differ in other carcinogenic exposures or socioeconomic conditions. There can be many subtle reasons why one population cannot adequately represent another. The major handicap is that these studies are not designed for elucidating any dose–response relationship.

While chromosomal injury detected in PBLs remains as a quantitative biodosimetry tool, there is no conclusive evidence that the exposure received in HNBR areas itself leads to any form of health detriment. Examples exist from China, Iran, or Brazil where elevated frequencies of dicentrics and rings were observed but no excess risk of cancer was detected [29, 43, 11].

Results of studies conducted in HNBR areas sometimes have been used to discuss the validity of the LNT extrapolation of dose–effect relationships in the low dose and low dose-rate range [74, 7, 75]. Some authors have interpreted the absence of an observed excess of cancers as support for a protective effect of radiation [76–78]. However, as discussed here, null findings are generally not informative.

Given the limitations of the HNBR studies conducted up to now, it appears highly desirable to not over-interpret findings. This review leads to the unavoidable conclusion that, with one exception, any assertions on studies of detrimental or protective effects from HNBR exposure appear premature. The only real conclusive evidence is that indoor radon studies indicate an elevation of lung cancer risk even for levels of exposure as low as 200 Bq m^{-3} [58].

Finally, it should be noted that above and beyond the unavoidable difficulties associated with study of exposure to HNBR, the estimation of excess cancer risk per unit dose will be extremely difficult to accomplish with high precision, due in part to the unknown shape of the dose response at very low doses.

6. Recommendations

Given the difficulties discussed in achieving adequate statistical power and eliminating biases and confounding factors as well as the difficulty in obtaining the retrospective dosimetry of the exposed persons, what types of investigations would likely yield new knowledge and which of those would be cost-effective to conduct? It seems feasible to focus on the documentation of environmental dose rates through environmental monitoring activities, and the establishment of a database of individual dose estimates for local residents. This should include both internal and external exposure, based on retrospective dosimetry measurements and calculations supplemented with actual residence histories. Also, the effects of non-radiation clastogens is an important factor, and data could be collected. As shown in the chromosome study in China [34], the large individual variations of confounding effects caused by non-radiation clastogens masked the effect of low dose radiation. That study indicates that in an epidemiologic study of cancer related to very low dose radiation, increasing the size of the cohort increases the individual variations and does not necessarily increase the statistical power.

A dose of 1 mGy produces one persistent DNA double-strand break in a small percentage of cells, and these breaks can be detected using γ-H2AX staining of the broken ends [79]. This is an extremely sensitive technique, and potentially could be used in the future as a

biomarker of such very low doses of HNBR. Other biological studies could include exploration of gene expression profiles associated with chronic low-level radiation exposure and the often-discussed possibility of an adaptive response.

To evaluate the important question whether a health risk is associated with residence in HNBR areas requires a well-established and very carefully coordinated programme. Despite the difficulties in conducting defensible epidemiologic investigations, the example of indoor radon studies shows that it is possible to demonstrate, directly in the general population, the existence of a risk associated with protracted low levels of natural environmental exposures. This result has been made possible primarily as a result of carefully designed epidemiologic studies based on individual data, and an international collaborative effort toward quality and standardisation of data collection. Also, without an accurate and complete control of smoking behaviour (the major confounder) this goal never would have been achieved.

If contemplated studies of HNBR were judged to be both feasible and informative, then following the example of the indoor radon studies, there would be a greater likelihood of conducting successful studies with directed or coordinated efforts across countries and the development and use of common protocols including those for individual dosimetry from external and internal sources. Using organ-specific dose estimates potentially affords the opportunity to characterise risks to specific organs, though adequate dosimetry is required that captures information on all sources (internal and external), taking into consideration exposures, occupancy factors, and movements across study areas with differing levels of contamination. Furthermore, as the integral dose received is time dependent, and as doses in these HNBR areas tend to be low, analyses would be more powerful if they used continuous lagged cumulative doses to specific organs for each subject, rather than groupings. Finally, the use of common core protocols across countries would allow for more direct comparison of results across studies and might also allow combined analyses, which would maximise the resultant information.

Since the lifetime risk from exposure in HNBR areas, even over many years of residence, is likely to be small except perhaps for very few numbers of people, it is critical to identify those health outcomes that can reasonably be studied in available populations and to use appropriate and sensitive epidemiological study designs. The conduct of nested case–control studies, with dose assessment on an individual level and collection of individual information on known as well as other possible risk factors for the diseases of interest, will be a useful tool for the evaluation of any potential health risks from low-level chronic radiation exposures.

References

[1] Eisenbud M and Gesell T 1997 *Environmental Radioactivity from Natural, Industrial, and Military Sources* (San Diego, CA: Academic) chapter 6 (Natural Radioactivity)

[2] Sohrabi M 1997 High radon levels in nature and in dwellings: remedial actions *Radon Measurements by Etched Track Detectors. Applications in Radiation Protection, Earth Sciences and the Environment* ed R Ilic and S A Durrani (Singapore: World Scientific) pp 225–42

[3] Sohrabi M 1998 The state-of-the-art on worldwide studies in some environments with elevated naturally occurring radioactive materials (NORM) *Appl. Radiat. Isot.* **49** 169–88

[4] ICRP 60 1991 1990 Recommendations of the International Commission on Radiological Protection *Ann. ICRP* **21** issues 1–3

[5] IBSS 1996 International basic safety standards for protection against ionizing radiation *Safety Series 115* International Atomic Energy Agency

[6] BEIR VII 2006 Health risks from exposure to low levels of ionizing radiation *Biological Effects of Ionizing Radiation (BEIR) VII Report* (Washington, DC: The National Academies Press)

[7] Tubiana M, Aurengo A, Averbeck D, Bonnin D, LeGuen B, Masse R, Monier R, Valleron A J and de Vathaire F 2005 *Dose–Effect Relationships and Estimation of the Carcinogenic Effects of Low Doses of Ionizing Radiation* Académie Nationale de Médecine (Paris: Institut de France-Académie des Sciences)

[8] Cullen T L and France E P 1977 *Int. Symp. on Areas of High Natural Radioactivity (Proc. Int. Symp. Poços de Caldas 1975)* Academia Brasileria de Ciencias Rio de Janeiro

[9] Veiga L H, Koifman S, Melo V P, Sachet I and Amaral E C 2004 Preliminary indoor radon risk assessment at the Pocos de Caldas Plateau, MG-Brazil *J. Environ. Radioact.* **70** 161–76

[10] Sachett I A 2002 Caracterização da Radiação Gama Ambiental em Áreas Urbanas Utilizando uma Unidade Móvel de Rastreamento *PhD Thesis* Universidade do Estado do Rio de Janeiro

[11] Veiga L H and Koifman S 2005 Pattern of cancer mortality in some Brazilian HBRAs *High Levels of Natural Radiation and Radon Areas: Radiation Dose and Health Effects* ed T Sugahara, Y Sasaki, H Morishima, I Hayata, M Sohrabi and S Akiba (Amsterdam: Elsevier) pp 110–3

[12] High Background Radiation Research Group C 1980 Health survey in high background radiation areas in China *Science* **209** 877–80

[13] Yuan Y L, Morishima H, Shen H, Koga T, Sun Q, Tatsumi K, Zha Y, Nakai S, Wei L and Sugahara T 1997 Recent advances in dosimetry investigation in the high background radiation area in Yangjiang, China *High Levels of Natural Radiation 1996, Radiation dose and Health Effects* ed T Wei, T Sugahara and Z Tao (Amsterdam: Elsevier) pp 223–33

[14] Sunta C M 1993 *Proc. Int. Conf. on High Level Natural Radiation Areas, Ramsar Iran* ed M Sohrabi, J U Ahmed and S A Durrani (Vienna: International Atomic Energy Agency) pp 71–86

[15] Thampi M V, Cheriyan V D, Kurien C J, Ramachandran E N, Karuppasamy C V, Koya P K, Birajalaxmi D, George K P, Rajan V K and Chauhan P S 2002 Cytogenetic studies in the high level natural radiation areas of Kerala *High Levels of Natural Radiation and Radon areas: Radiation Dose and Health Effects* ed W Burkhart, M Sohrabi and A Bayer (Amsterdam: Elsevier) pp 207–11

[16] Sohrabi M and Esmaeli A R 2002 *New Public Dose Assessment of Elevated Level Natural Radiation Areas of Ramsar (Iran) For Eidemiological Studies* ed W Burkart, M Sohrabi and A Bayer (Amsterdam: Elsevier) pp 15–24

[17] Sohrabi M and Babapouran M 2005 *New Public Dose Assessment From Internal and External Exposures In Low and Elevated Level Natural Radiation Areas of Ramsar, Iran* ed T Sugahara, Y Sasaki, H Morishima, I Hayata, M Sohrabi and S Akiba (Amsterdam: Elsevier) pp 169–74

[18] UNSCEAR 1993 1993 Sources and effects of ionizing radiation *1993 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly, with Scientific annexes* (New York: United Nations)

[19] Miles J 1998 Mapping radon-prone areas by lognormal modeling of house radon data *Health Phys.* **74** 370–8

[20] Dubois G 2005 An overview of radon surveys in Europe office for official publications of the European Communities *EUR 21892* Luxembourg

[21] ICRP 65 1993 Protection against radon-222 at home and at work *Ann. ICRP* **23/2**

[22] NRC 1995 1995 Radiation dose reconstruction for epidemiologic uses *National Research Council Report* (Washington, DC: National Academic Press)

[23] Lloyd D *et al* 1992 Chromosomal aberrations in human peripheral blood lymphocytes induced *in vitro* by very low doses of x-rays *Int. J. Radiat. Biol.* **61** 335–43

[24] IAEA 2001 *Cytogenetic Analysis for Radiation Dose Assessment: A Manual* (Vienna: IAEA)

[25] United Nations Scientific Committee on the Effects of Atomic Radiations (UNSCEAR) 2000 *Sources and Effects of Ionising Radiation Annex B Exposures from Natural Radiation Sources* (New York: United Nations)

[26] Hayata I 2005 Chromosomal mutations by low dose radiation versus those by other mutagenic factors *High Levels of Natural Radiation and Radon Areas: Radiation Dose and Health Effects* ed T Sugahara, H Morishima, M Sohrabi, Y Sasaki, I Hayata and S Akiba (Amsterdam: Elsevier) pp 17–20

[27] Lloyd D C, Edwards A A, Leonard A, Deknudt G, Natarajan A, Obe G, Palitti F, Tanzarella C and Tawn E J 1988 Frequencies of chromosomal aberrations induced in human blood lymphocytes by low doses of x-rays *Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med.* **53** 49–55

[28] Barcinski M A, Do C, Abreu M, De Almeida J C, Naya J M, Fonseca L G and Castro L E 1975 Cytogenetic investigation in a Brazilian population living in an area of high natural radioactivity *Am. J. Hum. Genet.* **27** 802–6

[29] Tao Z, Zha Y, Akiba S, Sun Q, Zou J, Li J, Liu Y, Kato H, Sugahara T and Wei L 2000 Cancer mortality in the high background radiation areas of Yangjiang, China during the period between 1979 and 1995 *J. Radiat. Res.* **41** (Suppl.) 31–41

[30] Zhou J, Tao Z, Sun Q, Akiba S and Zha Y 2005 Cancer and non-cancer epidemiological study in the high background radiation area of Yangjiang China *High Levels of Natural Radiation and Radon Areas: Radiation Dose and Health Effects* ed T Sugahara, Y Sasaki, H Morishima, I Hayata, M Sohrabi and S Akiba (Amsterdam: Elsevier) pp 97–101

[31] Wei L X, Zha Y R, Tao Z F T, He W H, Chen D Q and Yuan Y L 1990 Epidemiological investigation of radiological effects in high background radiation areas of Yangjiang, China *J. Radiat. Res.* **31** 119–36

[32] Jiang T *et al* 2000 Dose–effect relationship of dicentric and ring chromosomes in lymphocytes of individuals living in the high background radiation areas in China *J. Radiat. Res. (Tokyo)* **41** (Suppl.) 63–8

[33] Zhang W and Hayata I 2003 Preferential reduction of dicentrics in reciprocal exchanges due to the combination of the size of broken chromosome segments by radiation *J. Hum. Genet.* **48** 531–4

[34] Hayata I, Wang C, Zhang W, Chen D, Minamihisamatsu M, Morishima H, Wei L and Sugahara T 2004 Effect of high-level natural radiation on chromosomes of residents in southern China *Cytogenet. Genome Res.* **104** 237–9

[35] Zhang W, Wang C, Chen D, Minamihisamatsu M, Morishima H, Yuan Y, Wei L, Sugahara T and Hayata I 2004 Effect of smoking on chromosomes compared with that of radiation in the residents of a high-background radiation area in China *J. Radiat. Res.* **45** 441–6

[36] Kochupillai N, Verma I C, Grewal M S and Ramalingaswami V 1976 Down's syndrome and related abnormalities in an area of high background radiation in coastal Kerala *Nature* **262** 60–1

[37] Jaikrishan G, Andrews V J, Thampi M V, Koya P K, Rajan V K and Chauhan P S 1999 Genetic monitoring of the human population from high-level natural radiation areas of Kerala on the southwest coast of India. I. Prevalence of congenital malformations in newborns *Radiat. Res.* **152** S149–53

[38] Nair M K, Nambi K S, Amma N S, Gangadharan P, Jayalekshmi P, Jayadevan S, Cherian V and Reghuram K N 1999 Population study in the high natural background radiation area in Kerala, India *Radiat. Res.* **152** S145–8

[39] Jayalekshmi P, Gangadharan P, Binu V S, Nair R R K, Nair M K, Rajan B and Akiba S 2005 What did we learn from epidemiological studies in high background radiation area in India *High Levels of Natural Radiation and Radon Areas: Radiation Dose and Health Effects* ed T Sugahara, H Morishima, M Sohrabi, Y Sasaki, I Hayata and S Akiba (Amsterdam: Elsevier) pp 101–5

[40] Binu V S, Gangadharan P, Jayalekshmi P, Nair R R K, Nair M K, Rajan B and Akiba S 2005 The risk of lung cancer in HBR area in India—a case–control study *High Levels of Natural Radiation and Radon Areas: Radiation Dose and Health Effects* ed T Sugahara and Y Sasaki (Amsterdam: Elsevier)

[41] Cheriyan V D, Kurien C J, Das B, Ramachandran E N, Karuppasamy C V, Thampi M V, George K P, Kesavan P C, Koya P K and Chauhan P S 1999 Genetic monitoring of the human population from high-level natural radiation areas of Kerala on the southwest coast of India. II. Incidence of numerical and structural chromosomal aberrations in the lymphocytes of newborns *Radiat. Res.* **152** S154–8

[42] Forster L, Forster P, Lutz-Bonengel S, Willkomm H and Brinkmann B Natural radioactivity and human mitochondrial DNA mutations *Proc. Natl Acad. Sci. USA* **99** 13950–4

[43] Mosavi-Jarrahi A, Mohagheghi M, Akiba S, Yazdizadeh B, Motamedi N and Monfared A S 1990 Mortality and morbidity from cancer in the population living in high-level natural radiation area of Ramsar, Iran *Proc. Int. Conf. on High Levels of Natural Radiation (Ramsar, Iran)* ed M Sohrabi, J U Ahmed and S A Durrani (Vienna: IAEA) pp 106–9

[44] Fazeli T Z, Asai R Gh, Sohrabi M, Haydari A, Varzegar R, Zakeri F and Sheikholesllami H 1990 Cytogenetic studies of inhabitants of some high natural radiation areas of Ramsar, Iran *Proc. Int. Conf. on High Levels of Natural Radiation, Ramsar, Iran* ed M Sohrabi, J U Ahmed and S A Durrani (Vienna: IAEA) pp 459–64

[45] Ghiassi-Nejad M, Mortazavi S M, Cameron J R, Niroomand-rad A and Karam P A 2002 Very high background radiation areas of Ramsar, Iran: preliminary biological studies *Health Phys.* **82** 87–93

[46] Ghiassi-Nejad M, Zakeri F, Assaei R G and Kariminia A 2004 Long-term immune and cytogenetic effects of high level natural radiation on Ramsar inhabitants in Iran *J. Environ. Radioact.* **74** 107–16

[47] Stidley C A and Samet J M 1993 A review of ecologic studies of lung cancer and indoor radon *Health Phys.* **65** 234–51

[48] Magnus K, Engeland A, Green B M, Haldorsen T, Muirhead C R and Strand T 1994 Residential radon exposure and lung cancer—an epidemiological study of Norwegian municipalities *Int. J. Cancer* **58** 1–7

[49] Cohen B J 1995 Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products *Health Phys.* **68** 157–74

[50] BEIR VI 1999 The health effects of exposure to indoor radon *Biological Effects of Ionizing Radiation (BEIR) VI Report* (Washington, DC USA: The National Academies Press)

[51] Lubin J H 2002 The potential for bias in Cohen's ecological analysis of lung cancer and residential radon *J. Radiol. Prot.* **22** 141–8

[52] Lubin J H, Boice J D Jr and Samet J M 1995 Errors in exposure assessment, statistical power and the interpretation of residential radon studies *Radiat. Res.* **144** 329–41

[53] Field R W 2001 A review of residential radon case–control epidemiologic studies performed in the United States *Rev. Environ. Health* **16** 151–67

[54] Lubin J H 2003 Studies of radon and lung cancer in North America and China *Radiat. Prot. Dosim.* **104** 315–9
[55] Krewski D *et al* 2005 Residential radon and risk of lung cancer: a combined analysis of 7 North American case–control studies *Epidemiology* **16** 137–45
[56] Darby S *et al* 2006 Residential radon and lung cancer—detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14 208 persons without lung cancer from 13 epidemiologic studies in Europe *Scand. J. Work Environ. Health* **32** 1–83
[57] Kreienbrock L, Poffijn A, Tirmarche M, Feider M, Kies A and Darby S C 1999 Intercomparison of passive radon-detectors under field conditions in epidemiological studies *Health Phys.* **76** 558–63
[58] Darby S *et al* 2005 Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case–control studies *Br. Med. J.* **330** 223
[59] Kendall G M and Smith T J 2002 Doses to organs and tissues from radon and its decay products *J. Radiat. Prot.* **22** 389–406
[60] Laurier D, Valenty M and Tirmarche M 2001 Radon exposure and the risk of leukemia: a review of epidemiologic studies *Health Phys.* **81** 272–88
[61] Evrard A S, Hémon D, Billon S, Laurier D, Jougla E, Tirmarche M and Clavel J 2005 Ecological association between indoor radon concentration and childhood leukaemia incidence in France 1990–1998 *Eur. J. Cancer Prev.* **14** 147–57
[62] Bilban M and Vaupoti J 2001 Chromosome aberrations study of pupils in high radon level elementary school *Health Phys.* **80** 157–63
[63] Bilban M, Biban-Jakopin C and Vrhovec S 2001 Incidence of chromosomal aberrations and micronuclei in cave tour guides *Neoplasma* **48** 278–84
[64] Oestreicher U, Braselmann H and Stephan G 2004 Cytogenetic analyses in peripheral lymphocytes of persons living in houses with increased levels of indoor radon concentrations *Cytogenet. Cell Genet.* **104** 232–6
[65] Bauchinger M, Braselmann H, Kulka U, Huber R and Georgiadou-Schumacher V 1996 Quantification of FISH-painted chromosome aberrations after domestic radon exposure *Int. J. Radiat. Biol.* **70** 657–63
[66] Lindholm C, Makinodan T, Paile W, Koivistoinen A and Salomaa S 1999 Domestic radon exposure and the frequency of stable or unstable chromosomal aberrations in lymphocytes *Int. J. Radiat. Biol.* **75** 921–8
[67] Albering H J, Hageman G J, Kleinjans J C, Engelen J J, Koulishcer L and Herens C 1992 Indoor radon exposure and cytogenetic damage *Lancet* **340** 739
[68] Maes A, Poffijn A and Verschaeve L 1996 Case report: karyotypic and chromosome aberration analysis of subjects exposed to indoor radon *Health Phys.* **71** 641–3
[69] Wang C, Zhang W, Minamihisamatsu M, Morishima H, Yuan Y, Jiang T, Chen D, Wei L, Sugahara T and Hayata I 2005 Chromosome study in high background radiation area in Southern China *High Levels of Natural Radiation and Radon Areas: Radiation Dose and Health Effects* ed T Sugahara, Y Sasaki, H Morishima, I Hayata, M Sohrabi and S Akiba (Amsterdam: Elsevier) pp 3–7
[70] Zhang W, Wang C, Minamihisamatsu M, Wei L, Sugahara T and Hayata I 2008 Dose limits below which the effect of radiation on health becomes undetectable due to background variation *Mutat. Res.* **654** 96–9
[71] Lloyd D C, Lucas J N, Edwards A A, Deng W, Valente E, Hone P A and Moquet J E 2001 A study to verify a reported excess of chromosomal aberrations in blood lymphocytes of Namibian uranium miners *Radiat. Res.* **155** 809–17
[72] Wolf G, Arndt D, Kotschy-Lang N and Obe G 2004 Chromosomal aberrations in uranium and coal miners *Int. J. Radiat. Biol.* **80** 147–53
[73] Brenner D J *et al* 2003 Cancer risks attributable to low doses of ionizing radiation: assessing what we really know *Proc. Natl Acad. Sci. USA* **100** 13761–6
[74] Mifune M, Sobue T, Arimoto H, Komoto Y, Kondo S and Tanooka H 1992 Cancer mortality survey in a Spa area (Misasa, Japan) with a high radon background *Japan. J. Cancer Res.* **83** 1–5
[75] Tubiana M, Aurengo A, Averbeck D and Masse R 2006 Recent reports on the effects of low doses of ionizing radiation and its dose–effect relationship *Radiat. Environ. Biophys.* **44** 245–51
[76] Chen D and Wei L 1991 Chromosome aberration, cancer mortality and hormetic phenomena among inhabitants in area of high background radiation areas in China *J. Radiat. Res.* **2** (Suppl.) 46–53
[77] Wei L 1997 High background radiation areas: an important source of exploring the health effects of low dose ionizing radiation *High Levels of Natural Radiation. Radiation Dose and Health Effects* ed L Wei, T Sugahara and Z Tao (Amsterdam: Elsevier) pp 1–14
[78] Mortazavi S M J, Ghiassi-Nejad M, Karam P A, Ikushima T, Niroomand-Rad A and Cameron J R 1997 Cancer incidence in areas with elevated levels of natural radiation *Int. J. Low Radiat.* **2** 20–7
[79] Rothkamm K and Lobrich M 2003 Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses *Proc. Natl Acad. Sci. USA* **100** 5057–62