Radiation protection 125

Low dose ionizing radiation and cancer risk

Low Dose Ionizing Radiation and Cancer Risk

Proceedings of a scientific seminar
held in Luxembourg on 9 November 2000

CONTENTS

FOREWORD

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

The European Commission organises every year, in cooperation with the Group of experts referred to in Article 31 of the Euratom, a scientific seminar to discuss in depth a particular topic of radiation protection suggested by the Group.

There are difficulties and inherent limitations on obtaining significant information on the health effects of exposure to ionizing radiation from studies directly conducted at the levels of dose of principal interest for radiation protection. Therefore, the above-mentioned Directive is based on risk factors, extrapolated to lower doses and dose-rates from existing substantial information from epidemiological studies on the health effects of acute, high dose exposure of man to ionizing radiation.

The aim of the present seminar was to present elements for assessing whether the above-mentioned Directive, continues to ensure an adequate level of protection to the citizens of the European Union, based on an extrapolation to low doses of information on high doses, in the light of the information resulting from recent scientific research.

Leading scientists in this area, participating in the fourth and fifth European Research Framework Programmes in Radiation Protection, presented the latest information.

The seminar also dealt with leukaemia cluster nuclear installations, the assessment of their statistical significance and the relevant communication with interested groups of population.

UNSCEAR LIFETIME

CANCER RISK ESTIMATES

Colin R MUIRHEAD

National Radiological Protection Board, United Kingdom

Dale L PRESTON

Radiation Effects Research Foundation, Japan

Abstract

During the past few decades, several methods have been used to estimate cancer risks arising over a lifetime following radiation exposure. Following the simple time-constant relative and absolute risk models that were used to estimate solid cancer risks in earlier UNSCEAR reports, more sophisticated models have been considered recently – for example, to allow for variation over time in the relative risk. Also, additional data have become available in recent years for both the Japanese atomic bomb survivors and other irradiated groups, which has assisted in evaluating dose-response relationships and in estimating risks for specific types of cancer. This paper summarises the evaluation of cancer risks performed for the UNSCEAR (2000) report, with emphasis on the above issues and on uncertainties in risk estimation.

1. INTRODUCTION

The estimation of cancer risks following exposure to ionizing radiation has been the subject of several reports by international organisations such as the International Commission on Radiological Protection (ICRP, 1991) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1977, 1988, 1994) during the past few decades. These estimates have been based largely on data for survivors of the atomic bombings of Hiroshima and Nagasaki, supplemented in some instances by information from studies of medically-exposed groups. However, in order to arrive at risk estimates that are of more general applicability, extrapolations of the epidemiological data are required; for example, from groups with high and medium doses down to low doses, and from a limited period of follow-up to a lifetime.

This paper reviews current information on factors affecting lifetime cancer risks, and presents estimates derived for the new UNSCEAR (2000) report. In addition, uncertainties in these risk estimates are summarised.

2. TIME VARIATION IN RISKS

The most recent published follow-up of mortality in the Life Span Study (LSS) of Japanese A-bomb survivors covers the period up to the end of 1990, ie. 45 years after exposure (Pierce *et al*, 1996). Since most of the survivors aged 50 years or older at the time of the bombings had died by 1990, information on cancer risks in this group in essentially complete. In contrast, most of the survivors exposed as children were still alive at the time of the latest follow-up. Analyses indicate that most of the risk of radiation-induced leukaemia appears to have been expressed within about 40-45 years of exposure. A model developed by Preston *et al* (1994) under which the excess absolute rate varies by age at exposure and time since exposure has been used to calculate leukaemia risks in the UNSCEAR (2000) report. However, in contrast to leukaemia, a substantial proportion of the radiation-induced solid cancers in the LSS may not yet have occurred.

Previous evaluations of the risk of solid cancers, such as those in the UNSCEAR (1988) report, have concentrated on two models for the projection of risks over time. One was the time-constant absolute risk model, under which – following a minimal latent period of, say, 10 years following exposure – the excess absolute cancer rate remains constant throughout life. In contrast, under the time-constant relative risk model, the relative (or proportional increase in) risk remains constant throughout life. For both models, the excess risk (either on an absolute or relative scale) may vary by age at exposure and by gender. The relative risk model tends to predict larger lifetime risks than the absolute risk model. This is because baseline rates for most solid cancers increase with increasing age, and hence the excess absolute rate increases over time under the former but not the latter model.

As follow-up of the A-bomb survivors and other groups has progressed, it has become apparent that the time-constant absolute risk model does not describe the temporal pattern of risks for all solid cancers combined (e.g. UNSCEAR, 1994; Pierce *et al*, 1996). However, it is still unclear whether the time-constant relative risk model would apply throughout life. To reflect the uncertainty in the future pattern of risks, the UNSCEAR 1994 report gave the results of calculations based both on a time-constant relative model

and on models under which the relative risk ultimately decreases. Lifetime risks based on the latter models were about 20%-40% lower than those based on the former model (UNSCEAR, 1994).

To reflect uncertainty in the temporal pattern of solid cancer risks, two models have been considered in the UNSCEAR (2000) report. These models involve different formulations for the excess relative risk (ERR), i.e. the relative risk minus 1. One model is the time-constant relative risk model, under which the ERR depends on gender and age-at-exposure; hereafter this is referred to as the *age-at-exposure model*. Under the other model, referred to as the *attained-age model*, the ERR depends on gender and attained age, i.e. the age at death or incidence of cancer. Precise formulations for these models are given in UNSCEAR (2000).

The attained-age model was suggested by Kellerer and Barclay (1992) as a simple method of describing the age and temporal effects on solid cancer risks in the LSS. Whilst this model was derived empirically, there are similarities with a mechanistic model proposed by Pierce and Mendelsohn (1999), under which the ERR depends mainly on attained age. The following two simple examples, based on Kellerer and Barclay (1992), illustrate the differing predictions of the age-at-exposure and attained-age models.

(i)   Consider an acute exposure, either at age 20 or age 40 years. Under an age-at-exposure model for which the ERR decreases with increasing age at exposure (eg. as seen in the LSS (Pierce *et al*, 1996)), both the ERR and the excess absolute rate (EAR) of solid cancers at, say, age 60 years are larger if exposure occurs at age 20 than at 40 (see Figure 1). In contrast, under the attained-age model, the ERR and EAR at age 60 do not differ by age at exposure. Indeed, following a minimal latent period, age-specific risks under the attained-age model do not depend on age at exposure, as indicated in Figure 1. Both models predict higher lifetime risks for exposure at younger ages rather than at older ages. However, under the attained-age model this difference is due solely to the increased time for risks to be expressed if exposure occurs at young ages, whereas under the age-at-exposure model there is also an effect of age at exposure on the ERR.

(ii)   Suppose an acute exposure takes place at age 20 years. Under the age-at-exposure model, the ERR at age 40 is the same as that at age 60 (see Figure 1). In contrast, the ERR at age 40 under the type of attained-age model fitted to the A-bomb data is larger than that at age 60. More generally, the ERR decreases with increasing age under this attained-age model. The EAR at age 40 is smaller than that at age 60 under both models, as indicated, but the difference is not as great under the attained-age model as that under the age-at-exposure model.

Some idea as to the validity of these two models can be obtained by inspection of Figure 2, which shows the variation with gender, age at exposure and attained age in the ERR and EAR at 1 Sv for all solid cancers, based on the most recent LSS mortality data (Pierce *et al*, 1996). Under the age-at-exposure model, the ERR should not vary with attained age for a given age-at-exposure. However, Figure 2 shows that the ERR decreases with increasing attained age for exposure at age 10, although there is less variation with attained age for exposure at age 30 or 50. In contrast, Figure 2 is perhaps consistent with the prediction under the attained-age model, namely that the ERR would vary by attained age but not by age at exposure. Figure 2 also shows that the EAR increases with increasing attained age for each of the ages at exposure considered. However, for a given attained age, there is some suggestion that the EAR is higher for

exposure at younger than at older ages. This is more consistent with an age-at-exposure model than with an attained-age model, since the EAR should not depend on age at exposure under the latter model. Thus, while some of the patterns in Figure 2 agree partially with the predictions of the above two models, it appears that neither model describes all of the variation in risk. For example, Little *et al* (1997) have shown that the attained-age model does not describe fully the pattern of solid cancer incidence in the LSS up to 1987 (Thompson *et al*, 1994), although Pierce and Mendelsohn (1999) found that their mechanistic model – which approximates to the attained-age model – provides a reasonable fit to these data, after excluding breast and thyroid cancers.

Although neither the age-at-exposure model nor the attained-age model describes all of the variation in solid cancer risks in the LSS, both models provide a fairly reasonable fit to these data, and have been used in the UNSCEAR (2000) report for the purposes of calculating lifetime risks. Further details of the models and the method of calculation are given in that report. In particular, the effects of gender and either age at exposure or attained age on the ERR were taken to be same for specific solid cancer sites, except for those cancer sites for which there was strong evidence of different gender and age effects, eg. for liver and lung (UNSCEAR, 2000). Table 1 shows estimates of the risk of exposure-induced death (REID) in a Japanese population receiving an acute dose of 1 Sv. This measure of lifetime risk, which is defined by Thomas *et al* (1992), was also used in earlier reports by UNSCEAR (1988, 1994). Averaged over all ages at exposure, REID for all solid cancers combined is about 30% lower under the attained-age model than the age-at-exposure model. Similar results arise in the calculation of cancer incidence, as indicated in Table 1. The differences between the predictions of the two models are greatest for exposure at young ages, reflecting the different predicted patterns in the ERR many years after exposure. Clearly this uncertainty can be addressed only by continued long-term follow-up of the LSS and other large cohorts of persons with substantial exposures.

3.   DOSE-RESPONSE RELATIONSHIPS

Since the UNSCEAR (1994) report, more information has become available on the relationships between cancer risk and dose, both through continued follow-up of existing cohorts and by combined analyses of different studies. For example, in a combined analysis of studies of thyroid cancer incidence following external radiation exposure, Ron *et al* (1995) showed that a linear dose-response provided a good fit to data on childhood exposure, not only at high doses but also down to 0.1 Gy (low-LET). Results and issues pertinent to studies at low doses are covered in more detail in the paper by P Hall presented at this seminar, and are also discussed in the UNSCEAR (2000) report.

Much of the interest in recent years in dose-response relationships has centred on data from the LSS. Overall, risks for solid cancers in the LSS tend to be consistent with a linear dose-response relationship (Thompson *et al*, 1994; Pierce *et al*, 1996; Little and Muirhead, 1996, 1998; Pierce and Preston, 2000). Among individual types of solid cancer, only for non-melanoma skin cancer incidence is there a suggestion of non-linearity (Little and Muirhead, 1996; Ron *et al*, 1998). For leukaemia, a linear-quadratic model – such that the risk per unit dose is smaller at low rather than high doses – provides a significantly better fit than a linear model to data on both incidence (Preston *et al*, 1994) and mortality (Pierce *et al*, 1996) in the LSS.

7

The finding by Pierce *et al* (1996) of a statistically significant trend in the LSS mortality risks over the range 0-0.05 Sv for all solid cancers combined has attracted substantial attention. However, the interpretation of this result is not straightforward, since there is less evidence for such a trend over this dose range in the corresponding cancer incidence data (Thompson *et al*, 1994). For survivors with doses of 0.02-0.05 Sv, observed cancer rates were increased by 5%, compared with predicted value of 2% based on a linear model fitted over a wider range of doses. Pierce *et al* (1996) suggested that this difference might have been due to differential misclassification of death, namely a slight bias towards recording cancer rather than other causes on the death certificates of A-bomb survivors who were relatively close to the hypocentre of the bombings. This shows how small potential biases can affect the interpretation of low dose risks. A recent analysis by Pierce and Preston (2000), based on cancer incidence in the LSS up to 1994, has reported a statistically significant trend with dose over the range 0-0.1 Sv for all solid cancers combined. However, Pierce and Preston (2000) recommended that more attention be given to the comparison of results at low doses with those over a wider dose range; in particular, the incidence of solid cancers at doses down to 0.05-0.1 Sv does not appear to be over-estimated by linear dose-response estimates over the range 0-2 Sv or 0-4 Sv.

Investigations have been continuing for a number of years into the potential under-estimation of neutron doses in Hiroshima, based on the current DS86 dosimetry (eg. Straume *et al*, 1992; Kellerer and Nekolla, 1997). In the current absence of agreed revisions to these doses, it is difficult to be certain about the effect that they may have on dose-response relationships in the LSS. However, some analyses have been performed based on potential, but still not verified, changes to neutron doses. Both Little and Muirhead (2000) and Pierce and Preston (2000) have shown that allowing for such changes would increase the evidence for upward curvature in the dose-response for the incidence of all solid cancers combined, but that these data would still consistent be with linearity. Furthermore, Pierce and Preston (2000) estimated that the slope of the dose-response in Hiroshima might be decreased by only about 5-10%, although a definitive evaluation is not possible at present.

The UNSCEAR (2000) report did not review information on the effects of fractionation and dose rate in the same depth as the UNSCEAR (1993) report. However, some pertinent studies were considered in the new report. For example, both a study in Canada (Howe, 1995) and an earlier study in the USA (Davis *et al*, 1989) of tuberculosis patients with fractionated x-ray exposures from fluoroscopic examinations have not shown a raised risk of lung cancer, in spite of the high cumulative doses. Whilst these results differ from the raised risks seen in the A-bomb survivors (Thompson *et al*, 1994; Pierce *et al*, 1996), whose exposure was acute, the severity of tuberculosis may have affected the lung cancer findings in these patients. A combined analysis of fluoroscopy and A-bomb studies by Little and Boice (1999) indicated that fractionation may not have affected the risk of breast cancer in these studies, although this interpretation has been queried (Brenner, 1999). In addition to medical studies, more information has arisen from occupational studies. In particular, both a study of about 95,000 radiation workers in Canada, USA and UK (Cardis *et al*, 1995) and a study of approximately 125,000 workers in the UK (Muirhead *et al*, 1999) have shown some evidence of a dose-related increase in the risk of leukaemia, although the study populations overlapped. Whilst the statistical precision of these studies was limited, the findings were consistent with extrapolations from the LSS.

To conclude, in common with findings cited in the UNSCEAR (1994) report, data from the LSS are generally consistent with a linear dose-response model for solid cancers, and with a linear-quadratic model for leukaemia. Models of this type were therefore used for risk calculations in the UNSCEAR (2000) report. In particular, compared with the risks from an acute dose of 1 Sv, the risks from an acute dose of 0.1 Sv were predicted to be about a factor of 10 lower for solid cancers, and roughly a factor of 20 lower for leukaemia.

4.   SITE-SPECIFIC CANCER RISKS

The UNSCEAR (2000) report contains reviews of epidemiological data relating to radiation and each of 16 cancer sites. As well as the LSS data, information on studies of medical, occupational, natural and environmental exposures have been considered. The report includes tables that attempt to summarise findings from different studies for each of the cancer sites considered. However, it is difficult to synthesise these findings in order to produce a single estimate of risk for each site. Consequently, the site-specific estimates calculated in the UNSCEAR (2000) report are based on the LSS, which is the single most comprehensive and reliable source of information on cancer risks following whole body exposure of a population of all ages and both genders.

Figure III shows estimates of the ERR per Sv for various types of solid cancer, adjusted for age at exposure and gender, based on mortality in the LSS (Pierce *et al*, 1996). Whilst the variation between cancer sites in the ERR per Sv is not statistically significant, Pierce *et al* (1996) noted that this measure of risk may be expected to vary owing to differences in the aetiologies of the various cancer types. Although not presented here, the EAR per Sv would show greater variation between cancer sites than the ERR per Sv, once account is taken of differences in baseline rates between these cancer types.

A factor that can have a substantial influence on the calculation of site-specific risks is the method of transferring risks observed in the LSS in Japan to populations elsewhere in the world, which may have different baseline incidences of specific cancer types. Examples include the generally higher rates of lung and female breast cancer and lower rates of stomach cancer seen in western Europe and north America compared with Japan (Parkin *et al*, 1997). Epidemiological evidence that would permit a clear decision about the preferred method of transferring risks is generally lacking. An exception is breast cancer, where comparisons of data from the LSS and women with medical exposures in North America point to an absolute transfer of risks between populations (Land *et al*, 1980; Little and Boice, 1999). For some other sites, such as stomach, there are indications that a multiplicative or relative risk transfer would be appropriate, although the evidence is often not strong. Consequently, in common with the calculations performed by Land and Sinclair (1991) for Publication 60 of ICRP (1991), the UNSCEAR (2000) report contains site-specific risk estimates for five populations – China, Japan, Puerto Rico, UK and USA – using both relative and absolute transfer models.

Table 2 shows site-specific estimates of REID for cancer mortality following an acute whole-body dose of 1 Sv at age 30 years, both for males and for females, and for the above five populations and the two transfer methods (with the exception of Japan, for which the issue of risk transfer does not apply). The results given here are based on the attained-age risk projection model (see section 2). An exception concerns leukaemia, for which the risk model of Preston *et al* (1994) was used, together with an absolute transfer

in view of the general stability of baseline rates for leukaemia (excluding chronic lymphatic leukaemia (CLL)) across populations. As might be expected, the estimates of REID for solid cancer sites based on a relative transfer between populations are more variable than those based on an absolute transfer. A large contribution to the variation under the former method arises from the risks for lung and breast cancer, which are estimated to be higher in the USA and UK than in the other populations considered. Similar findings arise from calculations of cancer incidence rather than mortality. However, under the relative risk transfer, the variation between populations in the incidence risk for all cancers combined is not great as that for mortality (UNSCEAR, 2000).

For some types of cancer, such as bone, risk estimates were not calculated in UNSCEAR (2000) because of the small numbers in the LSS, although other studies have clearly demonstrated raised risks following exposures to high doses of radiation.   For example, studies of groups with medical or occupational exposures to radium have shown increased risks of bone malignancies (Fry, 1998; Nekolla *et al*, 2000). In contrast, there is little evidence of an association between radiation and, for example, non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma (Preston *et al*, 1994; UNSCEAR, 2000). Whilst the lack of evidence for certain cancer sites may reflect a paucity of information, e.g. small numbers for some rare cancers, the results for the lymphomas can be contrasted with the clear associations seen between radiation and another rare disease, namely leukaemia (excluding CLL).

In Publication 60, ICRP (1991) used estimates of site-specific cancer risks, based on the five populations considered here and both the relative and absolute risk transfer methods, together with weighting factors for non-fatal cancers and estimates for hereditary effects, in order to arrive at tissue weighting factors for radiation detriment. The site-specific risks described by ICRP (1991) generally fall within the range of the values calculated in the UNSCEAR (2000) report. However, as indicated above, site-specific risks can vary several-fold between populations under a relative risk transfer, although variations are less under an absolute risk transfer.

5.   DISCUSSION

Overall, the estimates of total cancer risk following radiation exposure at high doses and high dose rates derived in the UNSCEAR (2000) report are consistent with those in the corresponding 1994 report. Using the same approach taken in UNSCEAR (1994), namely applying an age-at-exposure model to a Japanese population of all ages, the lifetime risk of exposure-induced death from all solid cancers combined following an acute dose of 1 Sv is estimated in UNSCEAR (2000) as about 9% for males, 13% females and 11% averaged over genders (see Table 3). This last value compares with 10.9% in the UNSCEAR (1994) report. However, there are uncertainties in the new estimates, perhaps of the order of a factor of 2 higher or lower. For example, it can be seen from Table 3 that lifetime solid cancer risks based on an attained-age model are about 70% of those based on an age-at-exposure model. Furthermore, whilst lifetime solid cancer risks for those exposed as children might be twice the estimates for a population exposed at all ages, continued follow-up of groups such as the Japanese A-bomb survivors will be important in determining the pattern of future risks. In particular, such follow-up would help in examining to what extent the age-at-exposure and attained-

age models might describe the pattern of risks many years after exposure, and how these models may need to be refined.

As can be seen from Table 3, there is variation in estimates of total solid cancer risks made for different countries, particularly if relative risks rather than absolute risks are transported from the LSS in Japan. There is still relatively sparse information on the best method for transporting risks from Japan; additional combined analyses of data from the LSS and epidemiological studies of exposed groups in other countries would be of assistance in addressing this issue. The issue of how radiation-induced risks may vary by age, time, gender and population is even more problematic when specific cancer sites are considered, since there are often insufficient data to estimate these effects precisely for each site. As indicated in Table 2, notable differences can arise in estimates of site-specific risks between populations. Nevertheless, the site-specific values in UNSCEAR (2000) are generally consistent with the estimates made by ICRP (1991) and UNSCEAR (1994).

For all solid cancers combined, the LSS data are consistent with a linear dose-response. There are uncertainties in estimating risks at very low doses, in part because of limited statistical power but also because of the possible effects of residual bias or confounding. However, it was suggested in UNSCEAR (2000) that, as a first approximation, linear extrapolation of the solid cancer estimates at 1 Sv acute dose could be used to estimate risks at lower doses. Information on dose rate was not reviewed in detail in UNSCEAR (2000). An earlier report by the Committee (UNSCEAR, 1993) suggested a reduction factor of less than 3 for the risk per unit dose associated with exposures at low doses and low dose rates, when compared with that from exposures at high doses and high dose rates.

For leukaemia excluding CLL, the issues of transporting risks across populations and projection over time are less uncertain than for solid cancers, given that the international variation in baseline rates is relatively low and that the age and temporal patterns of risk are fairly well-defined. For either gender, the lifetime risk of exposure-induced leukaemia mortality is estimated in UNSCEAR (2000) as 1% following an acute dose of 1 Sv, which compares with 1.1% in UNSCEAR (1994) (see Table 3). Based on a linear-quadratic dose-response, the corresponding risk following an acute dose of 0.1 Sv is 0.05%, ie. a factor of 20 reduction associated a ten-fold decrease in dose, with no further reduction required for chronic exposures. The uncertainty in the leukaemia risk estimate may be on the order of a factor of 2, higher or lower.

Acknowledgements

References

Brenner, D. Commentary: Does fractionation decrease the risk of breast cancer induced by low-LET radiation? *Radiat Res*, **151**, 225-229 (1999).

Cardis, E, Gilbert, E S, Carpenter, L, *et al*. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res*, **142**, 117-132 (1995).

Davis, F G, Boice, J D, Hrubec, Z and Monson, R R. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res*, **49,** 6130-6136 (1989).

Fry, S A. Studies of US radium dial painters: an epidemiological classic. *Radiat Res*, **150**, S21-S29 (1998).

Howe, G R. Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the atomic bomb survivors study. *Radiat Res*, **142**, 295-305 (1995).

ICRP. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. *Ann ICRP*, **21** (1-3) (1991).

Kellerer, A M and Barclay, D. Age dependencies in the modelling of radiation carcinogenesis. *Radiat Prot Dosim*, **41**, 273-281 (1992).

Kellerer, A M and Nekolla, E. Neutron versus gamma-ray risk estimates. *Radiat Environ Biophys*, **36**, 73-83 (1997).

Land, C E, Boice J D, Shore, R E, Norman, J E and Tokunaga, M. Breast cancer risk from low-dose exposure to ionizing radiation: results from parallel analysis of three exposed populations of women. *J Natl Cancer Inst*, **65**, 353-376 (1980).

Land, C E and Sinclair, W K. The relative contributions of different organ sites to the total cancer mortality associated with low-dose radiation exposure. *Ann ICRP*, **22**(1), 31-57 (1991).

Little, M P and Boice J D. Comparison of breast cancer incidence in the Massachusetts fluroscopy cohort and in the Japanese atomic bomb survivors. *Radiat Res*, **151**, 218-224 (1999).

Little, M P, de Vathaire, F, Charles, M W, Hawkins, M M and Muirhead, C R. Variations with time and age in the relative risks of solid cancer incidence after radiation exposure. *J Radiol Prot*, **17**, 159-177 (1997).

Little, M P and Muirhead, C R. Evidence for curvi-linearity in the cancer incidence dose-response in Japanese atomic bomb survivors. *Int J Radiat Biol*, **70**, 83-94 (1996).

Little, M P and Muirhead, C R. Curvature in the cancer mortality dose response in Japanese atomic bomb survivors: absence of evidence of threshold. *Int J Radiat Biol*, **74**, 471-480 (1998).

Little, M P and Muirhead, C R. Derivation of low dose extrapolation factors from analysis of curvature in the cancer incidence dose response in the Japanese atomic bomb survivors. *Int J Radiat Biol*, **76**, 939-953 (2000).

Muirhead, C R, Goodill, A A, Haylock, R G E, *et al*. Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. *J Radiol Prot*, **19**, 3-26 (1999).

Nekolla, E A, Kreisheimer, M, Kellerer, A M, Kuse-Isingschulte, M, Gössner, W and Spiess, H. Induction of malignant bone tumours in radium-224 patients: risk estimates based on the improved dosimetry. *Radiat Res*, **153**, 93-103 (2000). (Erratum: *Radiat Res*, **153**, 848 (2000).)

Parkin, D M, Whelan, S L, Ferlay, J, Raymond, L and Young, J (eds). *Cancer Incidence in Five Continents*. Vol. VII. Lyon, IARC Scientific Publications No. 143 (1997).

Pierce, D A and Mendelsohn, M L. A model for radiation-related cancer suggested by atomic bomb survivor data. *Radiat Res*, **152**, 642-654 (1999).

Pierce, D A and Preston, D L. Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res*, **154**, 178-186 (2000).

Pierce, D A, Shimizu, Y, Preston, D L, Vaeth, M and Mabuchi, K. Studies of the mortality of A-bomb survivors. Report 12, Part 1. Cancer: 1950-1990. *Radiat Res*, **146**, 1-27 (1996).

Preston, D L, Kusumi, S, Tomonaga, M, *et al*. Cancer incidence in atomic bomb survivors. Part III: Leukemia, lymphoma and multiple myeloma, 1950-87. *Radiat Res*, **137**, S68-S97 (1994).

Ron, E, Lubin, J H, Shore, R E, *et al*. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res*, **141**, 259-277 (1995).

Ron, E, Preston, D L, Kishikawa, M, *et al*. Skin tumor risk among atomic-bomb survivors in Japan. *Cancer Causes and Control*, **9**, 393-401 (1998).

Straume, T, Egbert, S D, Woolson, W A, *et al*. Neutron discrepancies in the DS86 dosimetry system. *Health Phys*, **63**, 421-426 (1992).

Thomas, D C, Darby, S, Fagnani, F, Hubert, P, Vaeth, M and Weiss, K. Definition and estimation of lifetime detriment from radiation exposures: principles and methods. *Health Phys*, **63**, 259-272 (1992).

Thompson, D E, Mabuchi, K, Ron, E, *et al*. Cancer incidence in atomic bomb survivors. Part II. Solid tumors, 1958-87. *Radiat Res*, **137**, S17-S67 (1994).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Sources and Effects of Ionizing Radiation*. 1977 Report to the General Assembly, with annexes. New York, United Nations (1977).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Sources, Effects and Risks of Ionizing Radiation.* 1988 Report to the General Assembly, with annexes. New York, United Nations (1988).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Sources and Effects of Ionizing Radiation.* 1993 Report to the General Assembly, with annexes. New York, United Nations (1993).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Sources and Effects of Ionizing Radiation.* 1994 Report to the General Assembly, with scientific annexes. New York, United Nations (1994).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). *Sources and Effects of Ionizing Radiation.* 2000 Report to the General Assembly, with scientific annexes. New York, United Nations (2000).

Figure 1   Patterns with age in the excess relative risk (ERR) and excess absolute rate (EAR) for the examples cited in section 2, based on age-at-exposure and attained-age models.

————————	Exposure at age 20, age-at-exposure model
—·—·—·—·—·	Exposure at age 40, age-at-exposure model
------------	Exposure at age 20, attained-age model
····················	Exposure at age 40, attained-age model
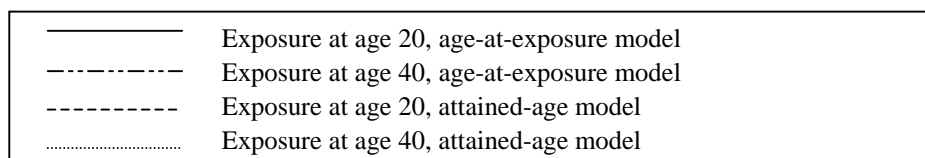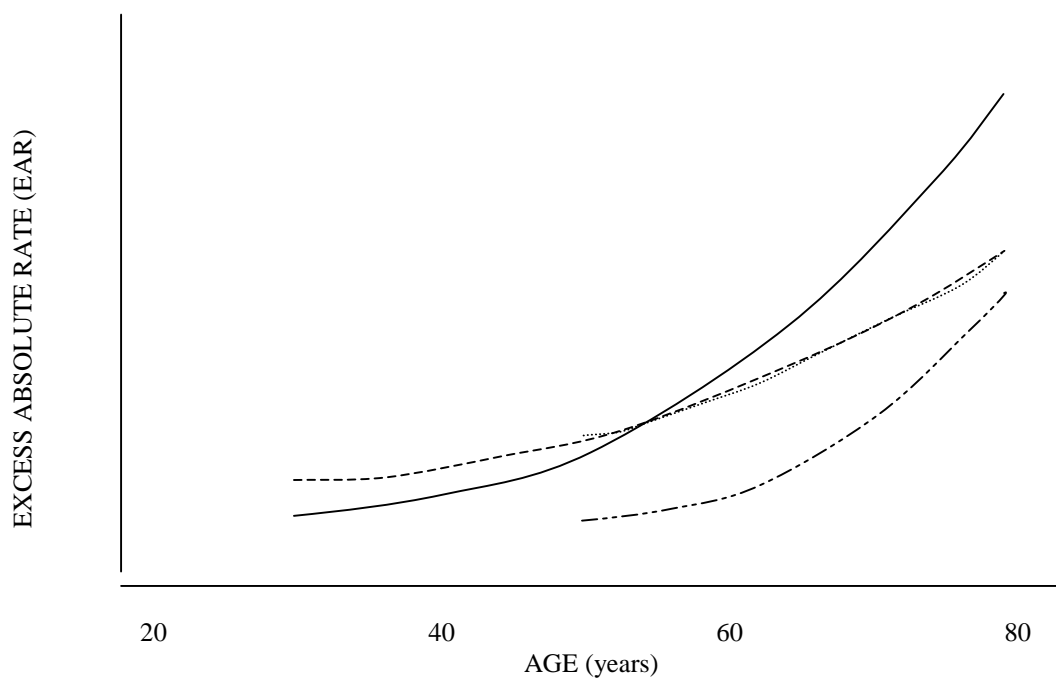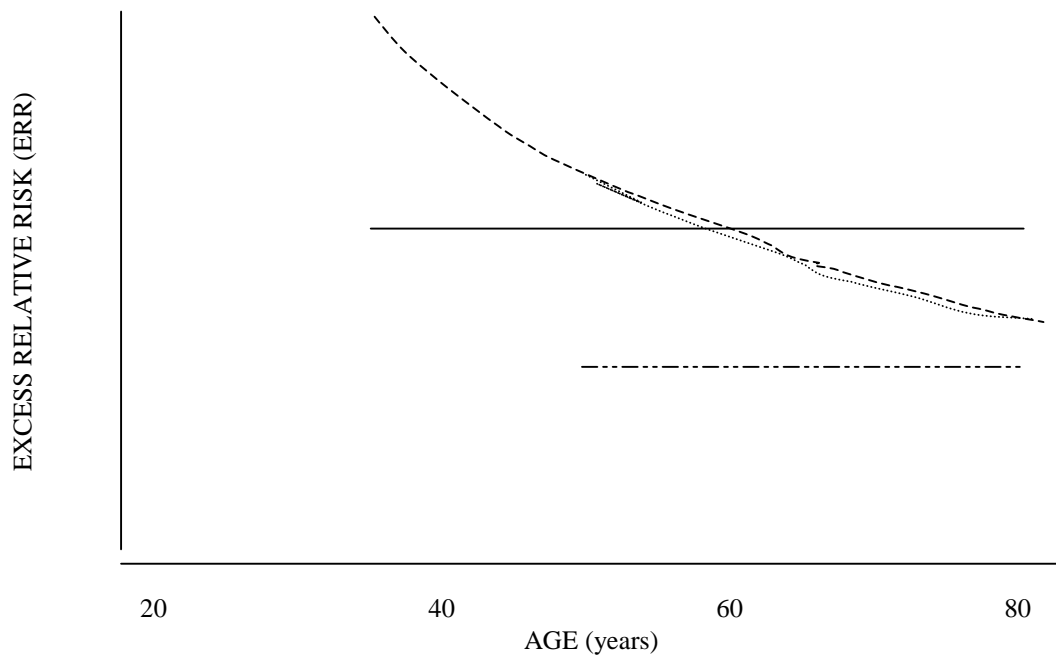
Figure 2   Excess relative risk (ERR) and excess absolute rate (EAR) at 1 Sv for solid cancer mortality among survivors of the atomic bombings in Japan (Pierce *et al*, 1996). The lines show the patterns of risk in the data.
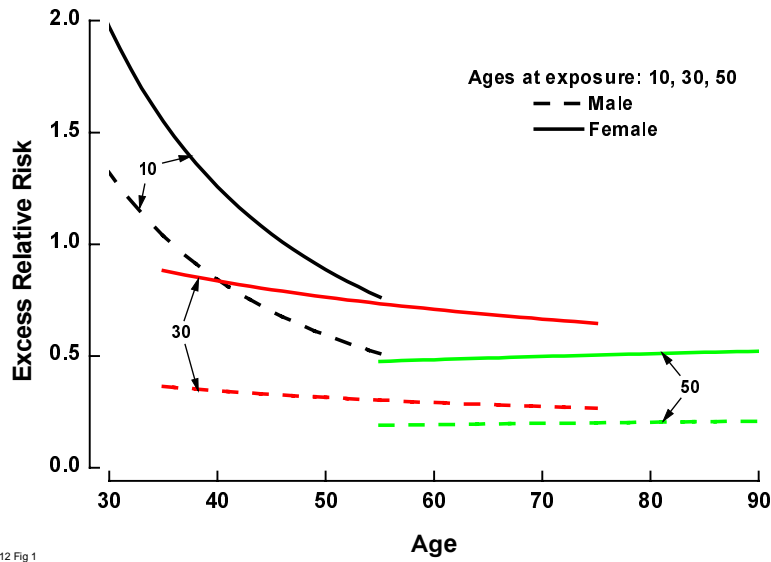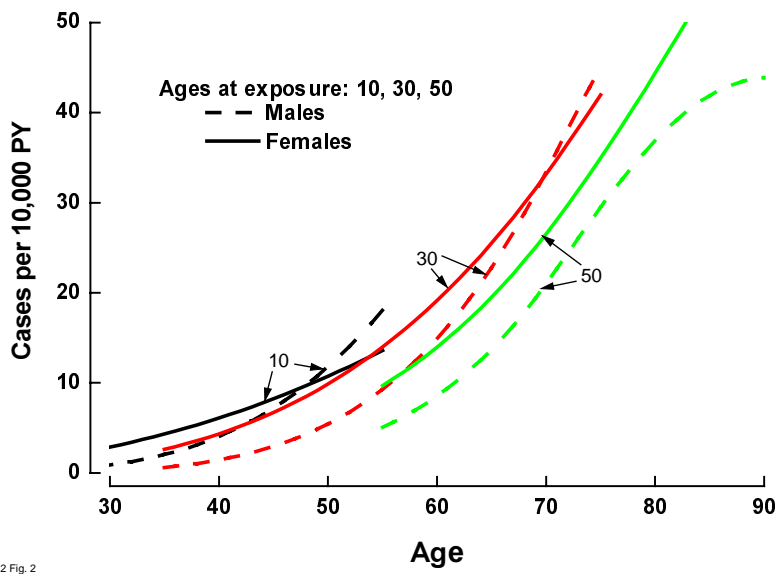
Figure 3 Excess relative risk for mortality (and 90% CI) from specific solid cancers and all solid cancers combined (horizontal line) among survivors of the atomic bombings in Japan (Pierce *et al*, 1996), standardised for females exposed at age 30 years
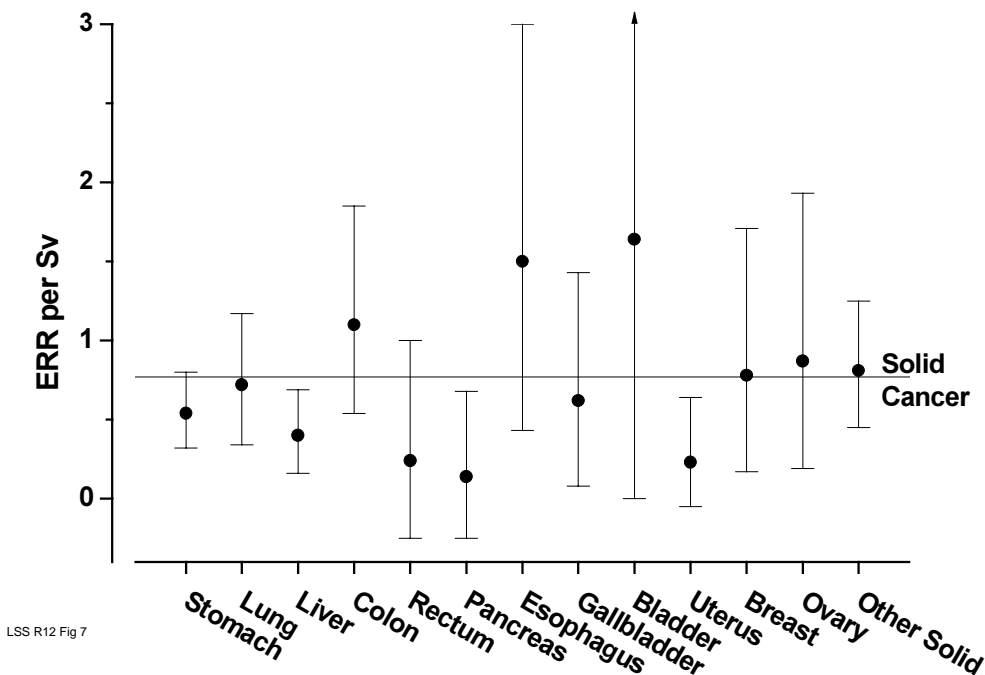
Table 1
Estimates of lifetime risk of exposure-induced death (REID) or cancer incidence for an acute whole-body exposure of 1 Sv to a Japanese population (UNSCEAR, 2000)

Projection model	Age at exposure (years)	REID (%)					
		Solid cancer mortality		Solid cancer incidence		Leukaemia incidence[1]	
		Male	Female	Male	Female	Male	Female
Age-at-exposure model	10	13.9	19.6	31.0	36.5	1.9	1.0
	30	8.6	11.9	15.4	18.8	0.8	0.9
	50	6.2	8.8	9.1	10.7	0.6	0.6
	All	9.5	12.9	18.6	21.0	1.0	0.7
Attained-age model	10	6.7	9.7	14.9	20.1	1.9	1.0
	30	6.7	9.5	13.3	18.1	0.8	0.9
	50	6.3	8.2	11.4	13.0	0.6	0.6
	All	6.2	8.5	13.3	16.2	1.0	0.7

Table 2
Estimates of REID for cancer mortality under the attained-age model, based on acute whole-body dose of 1 Sv at age 30 years (UNSCEAR, 2000)

| Cancer type	REID (%)								
	China		Japan	Puerto Rico		United Kingdom		United States	
	RR[2]	AR[3]		RR	AR	RR	AR	RR	AR
Males									
Oesophagus	2.6	0.6	0.7	1.2	0.7	0.5	0.8	0.3	0.7
Stomach	0.7	0.9	1.0	0.5	1.0	0.3	1.1	0.1	0.9
Colon	0.2	0.3	0.4	0.3	0.4	0.6	0.4	0.9	0.4
Liver	0.6	1.5	1.2	0.9	1.7	0.1	1.3	0.2	1.0
Lung	0.5	1.0	1.8	0.2	1.1	3.6	2.0	3.1	1.6
Breast	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Bladder	0.1	0.2	0.2	0.2	0.2	0.5	0.3	0.4	0.2
Other solid cancer	0.7	1.1	1.3	1.4	1.2	1.4	1.4	1.8	1.1
Solid cancer	5.3	5.6	6.7	4.8	6.4	7.1	7.3	6.8	5.9
Leukaemia[1]	0.5	0.5	0.9	0.5	0.5	0.7	0.7	1.0	1.0
Total	5.9	6.1	7.6	5.3	6.9	7.8	8.0	7.8	6.9
Females									
Oesophagus	3.2	0.4	0.6	1.3	0.5	0.7	0.6	0.2	0.5
Stomach	0.9	1.0	1.4	0.6	1.3	0.4	1.5	0.2	1.2
Colon	0.3	0.5	0.7	0.8	0.6	1.5	0.7	1.9	0.6
Liver	0.6	1.8	0.6	1.0	2.4	0.1	0.6	0.2	0.5
Lung	0.3	0.4	2.5	0.1	0.5	3.5	2.6	3.2	2.3
Breast	0.6	1.2	1.3	2.2	1.3	5.8	1.4	5.2	1.3
Bladder	0.1	0.2	0.2	0.3	0.2	0.5	0.3	0.3	0.2
Other solid cancer	1.8	1.8	2.3	2.8	2.3	2.8	2.5	3.2	2.2
Solid cancer	7.7	7.2	9.5	9.0	9.1	15.2	10.1	14.4	8.8
Leukaemia[1]	0.5	0.5	1.0	0.5	0.5	1.0	1.1	1.5	1.6
Total	8.1	7.6	10.4	9.6	9.7	16.2	11.2	15.9	10.3

---

1   Projection model of Preston *et al* (1994).
2   Relative risk transportation.
3   Absolute risk transportation.

Table 3
Estimates of lifetime risk of exposure-induced death (REID) or cancer incidence following an acute whole-body dose of 1 Sv to a population of all ages (UNSCEAR, 2000)

Projection model	Risk transport model	REID (%)														
		China			Japan			Puerto Rico			United Kingdom			United States		
		Male	Female	Both	Male	Female	Both	Male	Female	Both	Male	Female	Both	Male	Female	Both
Solid cancer mortality																
Age-at-exposure	RR [4]	8.2	11.7	9.9	9.5	12.9	11.2	7.3	11.9	9.6	9.5	19.3	14.4	8.5	16.4	12.5
	AR [5]	8.6	10.5	9.5	9.5	12.9	11.2	9.9	12.8	11.3	10.8	14.4	12.6	8.2	11.5	9.9
Attained-age	RR	4.9	7.1	6.0	6.2	8.5	7.4	4.4	7.9	6.1	6.6	13.5	10.1	6.2	12.4	9.3
	AR	5.3	6.8	6.0	6.2	8.5	7.4	6.1	8.2	7.2	6.7	9.1	7.9	5.4	7.6	6.5
UNSCEAR (1994)	RR				10.4	11.4	10.9									
Leukaemia mortality																
Age- & time-varying [6]	AR	0.94	0.56	0.75	1.04	0.79	0.92	0.91	0.52	0.72	1.02	0.87	0.95	1.13	1.25	1.19
UNSCEAR (1994)	AR						1.1									
Solid cancer incidence																
Age-at-exposure	RR	14.8	17.6	16.2	18.6	21.0	19.8	17.5	19.8	18.6	22.1	29.9	26.0	18.7	27.4	23.0
	AR	18.7	19.7	19.2	18.6	21.0	19.8	20.4	21.7	21.1	22.1	23.2	22.7	14.1	17.0	15.5
Attained-age	RR	10.2	13.8	12.0	13.3	16.2	14.7	8.6	13.8	11.2	12.9	22.6	17.8	12.3	23.1	17.7
	AR	13.0	14.7	13.8	13.3	16.2	14.7	14.0	16.2	15.1	14.6	17.0	15.8	10.7	13.5	12.1
Leukaemia incidence																
Age- and time-varying [3]	AR	1.27	0.84	1.06	1.00	0.73	0.87	1.29	1.12	1.21	1.19	0.96	1.08	1.24	0.94	1.09

---

4   Relative risk transportation.
5   Absolute risk transportation.
6   Model of Preston et al (1994).

CANCER RISKS AFTER EXPSOURE TO LOW DOSES OF IONIZING RADIATION –

CONTRIBUTION AND LESSONS LEARNT FROM EPIDEMIOLOGY

Per HALL

Karolinska Institutet, Sweden

ABSTRACT

Cancer risks associated with low doses of ionizing radiation are generally estimated by extrapolating results from intermediate or high doses, based on human and sometimes experimental data on dose-response relationships. The latest finding from the Japanese atomic bomb survivors reveals a linear and linear-quadratic relationship for solid tumours and leukaemia, respectively. Increased risks are detected at doses below 100 mSv but a threshold of 60 mSv can not be excluded.

In the present paper problems and sources used in determining cancer risks after exposure to low-levels of ionizing radiation will be discussed.

INTRODUCTION

Ionizing radiation is probably the most studied carcinogen there is, maybe with the exception of tobacco. Extensive studies of individuals exposed to ionizing radiation for a variety of reasons have identified two categories of radiation damage. The first is the acute or deterministic effect caused largely by cell killing requiring a threshold dose to be exceeded in order to manifest itself. The second type of damage occurs at late times after exposure and consists mainly of damage to the cell nucleus, causing radiation-induced cancer. If a germ cell is affected, hereditary effects in descendants have the potential to develop. In the case of radiation-induced hereditary effects, human studies have not provided quantitative estimates and are not considered in this presentation, neither is the acute or deterministic effect.

During the past decades extensive research on the long-term effects of ionizing radiation has been conducted and most epidemiological studies have involved populations and individuals exposed to high radiation doses. There is a number of populations under study and the most important source is the Japanese atomic bomb survivors. The data derived form this cohort has been used for determining exposure standards to protect the public and the workforce from the harmful effects of radiation. The standards were set by using modelling approaches to extrapolate from cancer risks observed following exposure to intermediate or high doses to predict changes in cancer frequency at low radiation doses. However, there are a number of difficulties and problems that influence the risk estimates at low doses.

The major exposure to low dose and low dose-rate radiation derives from medical tests, occupational, and environmental situations. The established model for determining carcinogenic effects at low doses in radiation protection is based on the hypothesis that the cancer incidence increases proportionally with radiation dose. A so-called linear no-threshold model has been adopted by most national and international bodies [1], [2]. The major implication of the no-threshold model for stochastic effects is that all doses, regardless of how low they are, must be considered potential carcinogenic but that some risk must be accepted at any level of protection.

A number of international organisations deal with the harmful effects of ionizing radiation and measures taken to avoid those effects. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has reviewed the stochastic effects of ionizing radiation in a number of reports [3], [4], [5], [1]. The aim of the International Commission on Radiological Protection (ICRP) is to provide a system for radiological protection applicable to occupational, medical, environmental, and exposure resulting from accidents. In Publication 60 of ICRP [2] it is stated that "The primary aim of radiological protection is to provide an appropriate standard of protection of man without unduly limiting the beneficial practices giving rise to radiation exposure".

DEFINITION OF LOW DOSES AND LOW DOSE RATES OF IONIZING RADIATION

Damage to the deoxyribonucleic acid (DNA) is considered the main initiating event by which radiation causes neoplastic development. The carcinogenic effect is caused either by direct interaction with ionizing particles or through the action of free radicals or other chemical products. There is evidence that damage to the DNA molecule caused by ionizing radiation results in the induction of a carcinogenic process and the critical

damage is supposed to be a double strand break in the DNA helix. A damaged cell could either be forced to program cell death (apoptosis) or the DNA could be repaired. However, if the repair mechanisms are failing or the repair is incomplete the induction of a tumour could start.

To interpret the cell response to low doses and low dose rate ionizing radiation these entities have to be defined. The UNSCEAR has covered this topic in earlier documents [6], [7]as well as in the latest report [1]. Various physical models has been developed evaluating dose-response relationships and microdosimetric arguments for defining low doses are based on statistical considerations of independent radiation tracks within cells or nuclei. The definition of low doses could also be based on direct observations in experimental or epidemiological studies. Through measurement of cell damage or death using human lymphocytes, linear and quadratic terms have been fitted the response and low doses have been judged to be 20-40 mSv. Animal studies, mainly using mice, studying induction of solid tumours and leukaemia at different dose rates of low LET radiation have also been used and a dose rate of 0.1 Gy min^{-1} has been suggested as a low dose rate regardless of total dose [7]. Data derived from epidemiological studies, mainly the atomic bomb survivors, suggests that for solid tumours and leukaemia, 200 mSv could be considered the upper limit for low dose exposure [1].

There are several mechanistic models taking cellular repair, transformation, survival, energy deposition, cellular and track structures, into consideration [1]. These models give quantitative estimates of available data sets and well as testing their validity. Mechanistic models have so far not been applied in radiation protection. Table 1 lists the various approaches to assess low dose and low dose rate from low LET radiation.

On the basis of physical and biological data the UNSCEAR committee concluded in their 1993 report [7] that a dose and dose rate effectiveness factor (DDREF) should be applied when assessing cancer risk at low doses or dose rates. The limits were doses below 200 mSv (regardless of dose rate) or when the dose rate is lower than 0.1 mSv min^{-1}, whatever the total dose. It was recommended that for tumour induction, the DDREF should be on the safe side "probably no more than 3". For high LET it seems to be little or no effect on the cancer risks of dose fractionation or dose rate at low to intermediate doses. No DDREF was therefore suggested for high LET radiation. A discussion on dose rates was not given in the latest UNSCEAR report [1].

The linear no-threshold model has gradually developed during the approximately 100 years that has passed since the first discovery of the carcinogenic effect of ionizing radiation in 1902 [8]. Before the Second World War radiation protection was based on the assumption of a "tolerance dose" below which no demonstrable harm could be measured [9]. However, in light of the emerging effects seen in the atomic bomb survivors, the concept of a threshold was abandon and the current belief is that exposure to ionizing radiation, no matter how small, carries a risk of detriment with the risk being proportional to the dose accumulated.

There has been extensive debate as to the shape of the dose response curve at doses below levels where effects could be measured. It has been postulated that by exposing cells to a low dose of ionizing radiation would make them less susceptible to a later high dose exposure. Animal studies have shown prolonged latency periods for leukaemia [10] and more efficient DNA repair [11] in mice previously exposed to an adapting dose compared to those not pre-irradiated. Even a beneficial effect of low dose of ionizing radiation, termed hormesis, has been discussed and the belief is that metabolic

detoxification and cell repair benefits from doses in the range of 1-50 mSv [12], [13]. It has even been suggested that atomic bomb survivors have had a beneficial effect of the exposure to ionizing radiation [14]. The hormesis hypothesis is intriguing, especially in the light of the adaptive response findings, but data must still be considered inconclusive.

EPIDEMIOLOGICAL AND STATISTICAL CONSIDERATIONS

Epidemiological studies are observational rather than experimental in their design. This is particularly true for what is called etiological epidemiological studies. It would, for instance, probably be very hard convincing any ethical committee of a study randomising individuals into different levels of exposure if the exposure would be considered harmful, e.g. ionizing radiation or smoking. On the other hand, people often, willingly or unwillingly expose themselves to harmful factors. In order to study the effect of such exposures we thus have to rely on populations that has been exposed due to reasons beyond our control. The epidemiological methods used therefore have one main goal and that is to create an "experimental-like" situation, e.g. making exposed and non-exposed groups as comparable as possible. In order to do this systematic and random errors have to be brought to a minimum (as done in any scientific study). The systematic error or validity of the study is dealt with through study design and the random error or precision through statistical methods reflected by the width of the confidence intervals for each risk estimate. The methodological and statistical considerations are briefly discussed below.

Various types of biases could distort an epidemiological study and a bias could be defined as a systematic error introduced in the study design. Four important problems, central to any epidemiological study, will be addressed –confounding, effect modification, selection bias, and information bias.

Confounding means that some risk factor, other than the one under study, is differently distributed among exposed and non-exposed. The effect of not controlling for confounding is that disease occurrence will differ independently of the effect under study. As an example, if an exposed group contains more men than women, this will lead to a difference in incidence of myocardial infarction (myocardial infarction being more common in men). If the exposure under study increases the risk of myocardial infarction then the difference in gender strengthens the effect and the result is a combination of the exposure under study and the effect of being a man. This problem can easily be controlled for by stratification, i.e. the effect of exposure being studied separately for men and women.

A special problem in populations medically exposed to ionizing radiation occurs if the underlying cause of exposure influences the effect under study, confounding by indication. In a study of approximately 36,000 patients receiving ^{131}I as a diagnostic procedure the overall risk (standardised incidence ratio, SIR) of a thyroid cancer was found to be 3.11 when the number of cancers were compared to what could be expected from the country as a whole (Hall, unpublished data). However, when the patients were divided in reason for referral and previous treatment the figures changed dramatically (Table 2). A total of 1,792 patients had received previous radiotherapy towards the neck region for a benign disorder and the SIR was 14.20 (95% confidence interval [CI] 8.64-19.77), 10,856 were examined under the suspicion of a thyroid tumour, SIR = 4.89 (95% CI 3.69 –6.08), and the reaming 23,795 patients were referred for other reasons and showed a non-significant increased risk of 1.40 (Table 2). This example shows the difficulty in using patients for risk estimations since previous therapy, underlying

disorder and/or reason for referral has to be taken into consideration. There are, however, certain positive aspects of patient cohorts, the dosimetry and follow-up is most often better than in for example occupational cohorts.

Effect modification means that the effect of an exposure differs between different groups. If females are more susceptible to ionizing radiation then men when it comes the induction of lung cancer, any study of radiation-induced lung cancer not stratifying for gender would thus give results difficult to interpret. Here again a stratified analysis solves the problem by studying the effect of the exposure for different strata, i.e. men and women separately. However, there are problems to take into consideration depending on how the effect of an exposure is measured. Lets us assume that the incidence of lung cancer in the non-exposed group is 1.0 per 1,000 person-years in women and 2.0 in men, and 3.0 and 4.0 in an exposed population, respectively (given the same exposure in both sexes). The absolute excess risk is 2.0 per 1,000 person-years for both men and women but the relative risk is 3.0 for women and 2.0 for men. When the effect is measured as a relative risk, gender is an effect modifier, which is not the case when the absolute risk is studied.

Bias can arise in a number of ways and a major problem is individuals lost to follow up in a study. If not identified, these persons will continue to contribute person years at risk without being at risk of developing a disease. Even the information on who has migrated can influence the results if the reason for migration is linked to exposure or effect. One example is the Techa River cohort consisting of approximately 28,000 individuals exposed to radioactive discharge from the Mayak nuclear facility in the Southern Urals, Russia [15]. Before the fall of the Soviet Empire there was little migration from the area that originally defined the study cohort. After 1992 migration has increased dramatically and if the migration was due to lack of health care in the areas along the river it could be a selection of individuals with life threatening disorders, such as cancer, that are leaving to seek medical attention.

When studying patients that were either diagnosed with or treated through the use of ionizing radiation one must always keep in mind that there is a reason why some patients are exposed and others not. As an example, approximately 36,000 patients were examined with radioiodine and the risk of a subsequent thyroid cancer was determined (Table 2). An overall three-fold risk was seen but the increase was confined to those either referred under the suspicion of a thyroid tumour or those receiving previous radiotherapy to the head and neck region. The conclusion was that the increased risk was unrelated to the radioiodine exposure.

Another problem emerge if the follow-up is related to exposure level, e.g. patients supposed to be exposed are screened for the disease under study. Information bias is a major problem when interpreting the recent findings of a sharply increased risk of thyroid cancer among children in the Chernobyl area. Screening programmes have increased the ascertainment of occult thyroid tumours through the use of ultrasound examination, a possibility discussed in one of the original reports [16]. Thyroid screening was locally organised in the most contaminated areas after the accident, but large-scale screening with ultrasound examination, supported by the Sasakawa and IPHECA programmes did not start until 1991 and 1992, [17], [18]. It is anticipated that 40%-70% of the diagnosed childhood thyroid cancer cases has been found through these programmes and this fact might be reflected in the findings published to date as shown in Table 3.

In the field of radiation epidemiology, three types of studies dominate cohort studies, case-control studies, and geographical correlation or ecological studies. A cohort study could in some instances be considered in analogue with an experiment, exposed and non-exposed groups are compared. A case-control study employs an extra step of sampling according to the outcome of individuals in the population. This extra step provides the case-control study to be more efficient than a cohort study of a whole population and also allows for better control of confounders, but the sampling procedure could increase the risk of a selection bias.

A cohort study consist of a defined population that is either defined and followed (prospective study) or constructed of a cohort of persons alive sometimes in the past (retrospective study) and followed forward in time. The cohort could consist of workers (e.g. nuclear power plant workers, Chernobyl recovery workers), patients or people living in certain areas. The exposure is given and the effect or outcome is measured. The weakness of a cohort study is that information, e.g. doses, vital status, cause of death, has to be gathered for all individuals which can be costly and time consuming. A cohort study is also highly dependent on reliable follow up possibilities, e.g. cause of death or cancer registries of uniform and high quality.

In a case-control study cases with a specified disorder are identified and exposure status in controls, defined as individuals not having the disease, is compared. If cases and controls are selected from a previous well-defined cohort, the case-control study is said to be nested within the cohort - a nested case-control study. The crucial step is to adequately select the controls since they should be representative of the exposure in the entire source population. A case-control study is used when it is difficult or too costly to obtain information on factors that might influence the result for the whole cohort or more detailed information is needed than available in the cohort setting.

An ecological correlation study examines the relationship between disease frequency and selected environmental factors, and place and time of residency are used as surrogates for actual exposure. This approach could be useful for generating hypothesis regarding aetiology of a disorder but the use of surrogate variables and the oversimplification of complex relationships limits the application of the method. As long as individual dosimetry is not performed it will always be unclear whether the cancer observed is associated with ionizing radiation or not. In most instances confounding factors are not taken into consideration and many risk factors, other than ionizing radiation, produce variation in cancer incidence and mortality. Smoking habits, demographic characteristics such as ethnicity, urbanisation, socio-economical factors, migration, and environmental factors including, are very seldom considered in ecological studies as has been pointed out elsewhere [19]. Other problems are lack of adequate information on number of cancers, accuracy of cancer diagnosis, natural variability in base line cancer incidence and autopsy rates, and a diluting effect through migration.

The following is an example of difficulties encountered when follow up data differs with regard to exposure in a cohort study. Ivanov et al [20], [21], has studied the cancer incidence in 142,000 Russian Chernobyl recovery operation workers. A significantly increased risk of leukaemia was found when the observed cases were compared with those expected from national incidence rates. However, the studies have been criticised for not using internal comparison [22], [23] because the increased medical surveillance and active follow-up of the emergency workers, coupled with underreporting in the general population, most likely influenced the results. In contrast, the same investigators [24] did not find an increased risk of leukaemia related to ionizing radiation in a case-

control setting. These findings suggest that, at least in the case of the Russian Federation, cancer incidence ascertainment in the exposed populations differ from that in the general population. Future epidemiological investigations might be more informative if they are based on appropriate internal comparison groups.

A specific feature of etiological epidemiological studies is that there is no possibility to tell if a specific carcinogen caused a cancer. Although molecular geneticists are identifying alterations that imply that a specific etiological agent caused a malignancy, no reliable tool is available today. We thus still have to depend on statistical differences between exposed and non-exposed populations. Models extrapolating risks for intermediate and high doses to low dose situations are necessary because of the inherited inability of epidemiological studies to evaluate small effects of the exposure variables.

In the future the strategy to pool studies in order to increase the statistical power will probably be most efficient since few new radiation exposed cohorts will be identified. Pooling of thyroid cancer studies [25] and nuclear workers [26] have been successful and contributed to our current belief in a carcinogenic effect at low doses. New data could derive from the exposed populations in the Southern Urals or from the Chernobyl recovery operation workers. To pool different data sets is, however, problematic and a number of difficulties has to be dealt with, among those, selection and follow-up of the cohort, base line cancer rates in different areas, measurement of outcome, etc.

From the Japanese atomic bomb survivor data is approximated that exposure to 2 Sv would double the risk of dying from cancer [27], i.e. a relative risk of 2. The ability of an epidemiological study to detect such an increase is good, even a causal association after exposure to 1 Sv (increased risk of approximately 50%) is possible to detect. However, after exposure to 100 mSv the risk is predicted to be 1.05 or an excess of 5%. As an example we could use the data presented by Dr. Muirhead where an approximately 10% increase in lifetime risk of dying from a cancer after exposure to 1 Gy is presented. In 1,000 persons, 18%, or 180 individuals, are supposed to die of a cancer (Swedish data). The 95% confidence interval of 180 is 153-207. If 1 Gy adds an additional 10%, i.e. 100 individuals, an epidemiologic study would probably have the ability to detect such an increase. However, if we want to measure the risk after exposure to 50 mSv the additional increase in death due to cancer is 0.5% or 5 cases, and we would not have the possibility to detect such an increase in 1,000 individuals. In order to have 80 percent power to detect an increase (i.e. rejecting the value 18% at 5% significance level) caused by 50 mSv we have to have a cohort of 57,000 exposed individuals, giving an extra 285 cases additional to those 10,260 expected to die form cancer. The atomic bomb survivors with confirmed doses are 86,000 [1]. In this exercise we have to keep in mind that the size of the study population is not the only prerequisite, an ability to control for confounding factors, consistent exposure data, and most importantly, reliable mortality registration and complete follow up, are also needed. If this is not the case we might chose to compare two groups where we expect 18% non-exposed individuals to die of cancer and 18.5% to die in a group exposed to 50 mSv. The problem is that we would need two comparable groups, the only difference should be the exposure to (50 mSv), consisting of 114,000 individuals each.

Factors, besides size of the study populations, that might influence the results of a radiation epidemiological study are listed and commented in Table 4.

CONTRIBUTIONS FROM EPIDEMIOLOGY

Information of radiation-induced cancer is available from a number of populations exposed to external radiation or incorporated radionuclides. Reason for exposure could be environmental, occupational or medical. The Life Span Study (LSS) is the single most important study of radiation carcinogenesis in human populations. It is a well-defined cohort of people who has been followed from 1950 in order to determine the cause of death, cancer incidence as well as other outcomes. The cohort is large, includes men and women of all ages, the dose range is substantial, and the individual doses well characterised. Weaknesses are that only those surviving 5 years are followed, haematological malignancies were recorded from 1950 and cancer incidence from 1958 and the effect of these selections are not known. The effect and contribution of the neutron component is also under debate.

When referring to the LSS one should keep in mind that the exposure was of high dose rate but that the majority of the individuals in the cohort were actually exposed to low doses. Close to 73% of the 86,572 individuals included was exposed to doses less than 50 mSv (weighted dose to the colon) and only 6% received more than 500 mSv [7]. An increased risk of dying from cancer was seen after exposure to < 50 mSv [27]. This finding was in conflict with previously published incidence data [28] and it was suggested that the difference could be explained by misclassification of causes of death for survivors close to the hypocenter. In a recent study, Pierce and Preston clarified the issue focusing on survivors exposed to doses less than 500 mSv [29]. The study was restricted to those individuals exposed within 3 km from the hypocenter since non-exposed outside this geographical limit had a 5% higher cancer incidence than non-exposed within the 3-km zone. The reason for this finding could be differences in distribution of risk factors related to urban-rural residency. A total of 7,000 cancers diagnosed in approximately 50,000 survivors between 1958 and 1994 yielded useful risk estimates and a statistically significant increased risk of cancer and leukaemia was found in the dose range 0-100 mSv.

Any epidemiological result must be interpreted in light of previous results, supporting experimental and animal evidence, and a possible dose-response relationship. The risk of solid tumours in the LSS seems to fit a linear model best [28], [27], [29], [30]. In Figure 1, taken from the latest publication by Pierce and Preston [29], it can be seen that the degree of linearity below 500 mSv is high. The conclusion was that there is little risk of low doses being overestimated by linear models from wider dose ranges and that there is direct statistical significant evidence of an increased risk below 100 mSv.

Little and Muirhead has addressed the possibility that the neutron component was underestimated [30]. If there is a true underestimation of the neutron component the upward curvature of the dose-response model for solid tumours is increased but data are still in agreement with a linear relationship. For leukaemia, a linear quadratic model, the risk per unit dose being lower at low doses than high doses, provides the best fit to the LSS data for both incidence [31] and mortality [27]. Later studies by Little and Muirhead revealed an even more pronounced upward curvature for leukaemia [30].

There has been considerable debate on the possibility of a dose below which there is no excess risk, a threshold. The threshold discussion is probably even more relevant after low dose rate exposure since protracted exposure might theoretically allow for molecular repair. However, the latter issue is not possible to address in the LSS studies. The

threshold model usually considered, the supposed threshold being 0 Sv, gives an upper limit to the confidence interval of 60 mSv in the latest LSS finding [29].

The data on dose-response provided by the atomic bomb survivors provide no clear low dose reduction factor for solid tumours or a factor very close to 1 [1]. As Little and Muirhead has recently shown [30], after taking uncertainties of dose estimates into consideration, the dose-response for leukaemia fitted a linear-quadratic relationship and it was concluded the best estimate of a reduction factor for leukaemia would be 2 [1]. Other studies regarding the dose-response relationship are females examined by repeated fluoroscopies [32], [33] where the risk of breast cancer was found to linearly relate to the absorbed breast tissue dose. Leukaemia risk in women given radiotherapy for cervical cancer the risk of leukaemia was consistent with a linear dose-response relationship, although a quadratic term could not be excluded [34].

The childhood thyroid gland is, besides red bone marrow, and premenopausal female breast, one of the most radiosensitive organs in the body [1]. Studies of thyroid cancer risks are therefore of importance when examining risks at low doses. Age at exposure is the strongest modifier of risk; a decreasing risk with increasing age has been found in several studies [25], [28]. Among survivors of the atomic bombings, the most pronounced risk of thyroid cancer was found among those exposed before the age of 10 years, and the highest risk was seen 15-29 years after exposure and was still increased 40 years after exposure [28]. The carcinogenic effect of ^{131}I is less understood, and the effects of radioiodine in children have never been studied to any extent, since medical examinations or treatments rarely include children [35]. In a pooled analysis by Ron et al., including 7 cohorts of children exposed to external photon radiation [25], the excess relative risk was 7.7 Gy^{-1} (95% CI: 2.1-28.7) which is the highest value found for any organ. The study included approximately 700 thyroid cancer cases and linearity was found to describe the dose response best even down to doses of 100 mSv.

Several studies of nuclear industry workers have been conducted and one of the largest includes 124,743 workers from the United Kingdom and a second analysis of the cohort was recently published [36]. No increased risk of solid tumours was detected but a borderline significant risk of leukaemia (excluding chronic lymphatic leukaemia) resembling the central estimate of the LSS data [1]. It was concluded that the study provided some evidence of an elevated risk of leukaemia associated with occupational exposure to radiation and that the data was consistent with risk estimates of the ICRP report 60 [2]. In a combined analysis of workers from Canada, United Kingdom, and United States, including 95,673 workers, a total of 3,975 deaths due to cancer, 119 due to leukaemia, were found [26]. The risk of leukaemia just reached significance, excess relative risk being 2.18 Sv^{-1} (90% CI 0.1-5.7) and it was concluded that the current radiation risk estimates for low dose exposure was not appreciably in error.

The major exposure to ionizing radiation received by mankind comes from natural background radiation and it is a continuing and inescapable feature of life. The exposure originates from two sources, high-energy cosmic ray particles from outer space and radioactive nuclides that originate from the earth crust. The magnitude of the exposure is dependent on residency and occupation. Altitude above sea level determines the dose received from cosmic radiation, while radiation from the ground depends on the local geology, construction and ventilation of houses. Living at a high altitude can lead to a 5-fold increased dose, while dose dependent on the local geology can vary with a factor of

100. The average annual effective dose from natural sources for all humans on earth is estimated to be 2.4 mSv, where 1.3 mSv derives from exposure to radon [7].

By using the models based on the Committee on the Biological Effects of Ionizing Radiation [37]. Darby calculated the fraction of malignancies in the US population that were associated with the natural background radiation [38]. It was predicted that 11% of the deaths to leukaemia and 4% of deaths from solid tumours were caused by postnatal exposure to natural radiation other than radon. However, a number of studies during the years have failed to identify any increased risk of cancer or leukaemia due to background irradiation [39], [40], [41], [42]. In the Yangjiang province in China thorium-containing monazites have been washed down from the nearby heights and raised the background radiation level 3 times compared to adjacent areas of similar altitude. Approximately 80,000 individuals live in the high background areas and the annual dose to the red bone marrow was estimated to be 1.96 mSv compared to 0.72 mSv in the low dose, control area. When comparing overall cancer mortality and risk of dying from leukaemia, breast cancer and lung cancer, non-significant lower rates were seen in the high background areas [43],[44], [45], [46]. The correlation between cosmic radiation and cancer has been studied [47], [48] but no increased risks of leukaemia or cancer were found to be related to altitude.

The existence of a causal relation between prenatal exposure to ionizing radiation and childhood leukaemia remains controversial. No radiation-related excess of leukaemia has been identified among the approximately 3,000 atomic bomb survivors exposed in utero [49], [50]. In the 1950s, Stewart et al. [51] reported that prenatal radiation following diagnostic x-ray was associated with a subsequent increased risk of leukaemia and solid tumours during childhood and the report was followed by others [52], [53], [54] and contributed to major changes in medical practice. However, the presence of a causal relation still remains a subject of debate. Although major case-control studies, together with meta-analysis, consistently have shown a small risk increase for childhood leukaemia following a history of prenatal radiation [55],[56], [57], most cohort studies have not supported this association [53]. Early case-control studies were criticised for selection bias, since no adjustment was made for potential confounders such as concomitant disease in the mother and/or the foetus, or for recall bias as exposure information was based on interviews of parents of affected children. There is still no conclusive evidence that exposure to low dose of ionizing radiation in childhood increases the risk of leukaemia.

Chelyabinsk, located in the Southern Urals, was one of the former Soviet Union's main military production centres, including production of plutonium at the nuclear facility Mayak in the closed city of Ozersk. Accidents, nuclear waste disposal, and day to day operation of the Mayak reactor and radiochemical plant contaminated the Techa River. The period of highest releases was 1949-56, with a peak in released activity in 1950-51. In the period 1949-1956 a total of 7.6×10^7 m^3 of liquid wastes with a total radioactivity of 1.2×10^{17} Bq was released into the Techa-Isset-Tobol River system. In 1957, a nuclear waste storage exploded due to a chemical reaction, the Kystym accident.

Large populations were exposed to external gamma radiation, largely due to ^{137}Cs, and internal radiation, mostly due to intake of ^{90}Sr and ^{137}Cs through ingestion during a protracted period of time. At the time of the release there were 39 settlements located along the banks of the Techa River and the total population was 26,500. The individuals were not informed about the releases and the protective measures implemented (evacuations of the population, imposing restrictions on the use of flood lands and river

water in agricultural production and for domestic purposes) proved to be ineffective and implemented too late [58]. Large efforts have been taken, mainly by Japanese, US, and European scientists in collaboration with Russian colleagues, to increase the quality of the data, e.g. increase number of individuals with known vital status, cause of death, and residency. The doses received by the different groups have been extensively revised during the past years. For the Techa River inhabitants a new dosimetry system has been developed termed the Techa River Dosimetry System-2000 [59], [60].

Those exposed as a consequence of the operations at the Mayak nuclear facility has the potential of increasing our knowledge of effects of low dose and low dose rate exposure in the future. The cohort is large, have been intensively monitored for the past 40 years, and individual doses are available. Efforts so far has been focused on increasing quality of the material, in the coming years valid results will emerge.

A group that might contribute to future knowledge of the carcinogenic effects is the Chernobyl recovery operation workers. About 600,000 persons, civilian and military, have received special certificates confirming their status as recovery operation workers in the Russian Federation, Belarus, and Ukraine [1]. In all, 226,000 persons were employed in the 30-km zone in 1986-87. The remaining workers, who generally received lower doses, worked outside the zone or in 1988-90. An additional 17,705 workers were recorded in the registries of the Baltic countries. Estimates from external gamma radiation were measured with individual dosimeters, group dosimetry (an individual dosimeter was assigned to one person in the group), and through time-and-motion studies [1]. Unfortunately little is known about the doses for the first two months after the accident. It has been estimated that the annual average dose was 170 mSv (1986), 130 mSv (1987), 30 mSv (19988), and 15 mSv (1989). However, a number of uncertainties must be addressed, e.g. different dosimeters were used without intercalibration, a high number of doses were very close to the dose limit, and a high number of rounded figures (0.1, 0.2 or 0.5 Sv) were found. Using biological dosimetry for validation there seems to little risk of a systematical overestimation of the doses [1]. Fourteen years have passed since the accident and any increased risk of solid tumours due to the ionizing radiation should appear within the coming years. But, as discussed elsewhere in the paper, there are a number of methodological difficulties to consider before conducting studies of this highly selected group of healthy young men.

DISCUSSION

Radiation protection guidelines for solid tumours are dependant on a linear non-threshold model based on findings from the atomic bomb survivors, underlying that the slope should be divided by two at low doses and dose rates [2]. However, the most recent findings from the Life Span Study indicate that the reduction at low doses for leukaemia should probably be 2 and for solid tumours closer to 1 [29], [30]. On should keep in mind that the "dose-response" relationships and figures discussed are simplifications of a more complex relationship since a dose-response is not a number but a pattern of risk depending on sex, age ate exposure, and time since exposure.

In the atomic bomb survivors [29], [30], nuclear workers [36], [26] and in children exposed to external photon radiation developing thyroid cancers [25] it has been shown that the risk of cancer is increased even at doses below 100 mSv. We don't know if there are radiation doses below which there is no significant biological change or below which

the damage induced can be effectively dealt with by normal cellular processes. The Japanese data could not exclude a threshold of 60 mSv [29], [30].

The possibility of ecological studies of environmental exposure to ionizing radiation to contribute to our knowledge on effects of low dose exposure is limited. The effects of natural background radiation are low and other risk factors will distort the results.

Advances in molecular biology and genetics will hopefully increase the likelihood of finding the "true" effect of ionizing radiation at low doses. Research will focus on understanding cellular processes responsible for recognising and repairing normal oxidative damage and radiation-induced damage. If the damage and repair induced by low dose radiation is the same as for other oxidative damage, it is possible that there are thresholds of damage that the body can handle. On the other hand, if the damage from ionizing radiation is different from normal oxidative damage, then its repair, and the hazard associated with it, may be unique and a threshold will never be identified.

References

1. UNSCEAR. United Nations ScientificCommittee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 2000. Report to the General Assembly, with scientific annexes. New York: United Nations; 2000.
2. ICRP-60. International Commission on Radiological Protection. 1990 Recommendation of the International Commission on Radiological Protection. Annals of the ICRP, Vol 21, Publication 60. Oxford: Pergamon Press; 1991.
3. UNSCEAR. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation, with Annexes. New York: United Nations; 1977.
4. UNSCEAR. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, Effects and Risks of Ionizing Radiation. 1988 Report to the General Assembly, with Annexes. New York: United Nations; 1988.
5. UNSCEAR. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes. New York: United Nations; 1994.
6. UNSCEAR. United Nations Scientific Committee on the Effects of Atomic Radiation. Genetic and somatic effects of ionizing radiation. 1986 Report to the General Assembly, with Annexes. New York: United Nations; 1986.
7. UNSCEAR. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 1993 Report to the General Assembly, with scientific annexes. New York: United Nations; 1993.
8. Frieben A (1902) Demonstration eines Cancroides des rechten Handruckens,das sich nach langdauernder Einwirkung von Roentgenstrahlen enwikelt hat. Forthschr Röntgenstr 6: 106-111
9. Kathren RL (1996) Pathway to a paradigm: the linear nonthreshold dose-response model in historical context. The American Academy of Health Physics 1995 Radiology Centennial Hartman Oration. Health Phys 70: 621-35

10. Mitchel RE, Jackson JS, McCann RA, Boreham DR (1999) The adaptive response modifies latency for radiation-induced myeloid leukaemia in CBA/H mice. Radiat Res 152: 273-9

11. Ikushima T, Aritomi H, Morisita J (1996) Radioadaptive response: efficient repair of radiation-induced DNA damage in adapted cells. Mutat Res 358: 193-8

12. Luckey TD (1982) Physiological benefits from low levels of ionizing radiation. Health Phys 43: 771-89

13. Macklis RM, Beresford B (1991) Radiation hormesis. J Nucl Med 32: 350-9

14. Mine M, Okumura Y, Ichimaru M, Nakamura T, Kondo S (1990) Apparently beneficial effect of low to intermediate doses of A-bomb radiation on human lifespan [see comments]. Int J Radiat Biol 58: 1035-43

15. Kossenko MM, Degteva MO, Vyushkova OV, Preston DL, Mabuchi K, Kozheurov VP (1997) Issues in the comparison of risk estimates for the population in the Techa River region and atomic bomb survivors. Radiat Res 148: 54-63

16. Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D (1992) Thyroid cancer after Chernobyl. Nature 359: 21-22

17. Yamashita S, Shibata Y, editors. Chernobyl: A Decade. Proceedings of the Fifth Chernobyl Sasakawa Medical Cooperation Symposium, Kiev, Ukraine, October 1996. Amsterdam: Elsevier Science B.V.; 1997.

18. Souchkevitch GN (1996) Main scientific results of the WHO International Programme on the Health Effects of the Chernobyl Accident (IPHECA). World Health Stat Q 49: 209-12

19. Modan B (1991) Low-dose radiation epidemiological studies: an asessment of methodological problems. Review. Ann. ICRP 22: 59-73

20. Ivanov VK, Tsyb AF, Gorsky AI, Maksyutov MA, Rastopchin EM, Konogorov AP, Korelo AM, Biryukov AP, Matyash VA (1997) Leukaemia and thyroid cancer in emergency workers of the Chernobyl accident: estimation of radiation risks (1986-1995). Radiat. Environ. Biophys. 36: 9-16

21. Ivanov V (1996) Health status and follow-up of liquidators in Russia. In: (Karaoglou A, Desmet G, Kelly GN, Menzel HG) Karaoglou A, Desmet G, Kelly GN, Menzel HGKaraoglou A, Desmet G, Kelly GN, Menzel HGs.| Book Title. Publisher, |:Edition ed| City, Pages|

22. Boice JD, Jr. (1997) Leukaemia, Chernobyl and epidemiology. Invited editorial. J. Radiol. Prot. 17: 129-133

23. Boice JD, Jr., Holm L-E (1997) Radiation risk estimates for leukaemia and thyroid cancer among Russian emergency workers at Chernobyl. Letter. Radiat. Environ. Biophys 36: 213-214

24. Ivanov VK, Tsyb AF, Konogorov AP (1997) Case-control analysis of leukaemia among Chernobyl accident emergency workers residing in the Federation, 1986-1993. J Radiol Prot 17: 137-157

25. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD, Jr. (1995) Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 141: 259-277

26. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, Beral V, Cowper G, Douglas A, Fix J, Fry SA, Kaldor J, Lavé C, Salmon L, Smith PG, Voelz GL, Wiggs LD (1995) Effects of low doses and low dose rates of exernal ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat. Res. 142: 117-132

27. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K (1996) Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990 [see comments]. Radiat Res 146: 1-27

28. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, Preston DL (1994) Cancer incidence in atomic bomb survivors. Part II: Solid tumours, 1958-1987. Radiat Res 137: S17-S67

29. Pierce DA, Preston DL (2000) Radiation-related cancer risks at low doses among atomic bomb survivors. Radiat Res 154: 178-86

30. Little MP, Muirhead CR (2000) Derivation of low-dose extrapolation factors from analysis of curvature in the cancer incidence dose response in Japanese atomic bomb survivors. Int J Radiat Biol 76: 939-53

31. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, Nonaka H, Thompson DE, Soda M, Mabuchi K (1994) Cancer incidence in atomic bomb survivors. Part III: Leukaemia, lymphoma and multiple myeloma, 1950-1987. Radiat. Res. 137: S68-S97

32. Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinner PJ, Risch HA, Preston DL (1989) Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. N Engl J Med 321: 1285-1289

33. Boice JD, Jr., Preston D, Davis FG, Monson RR (1991) Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat. Res. 125: 214-222

34. Boice JD, Jr., Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, Austin DF, Bosch A, Cookfair DL, Krementz ET, others (1987) Radiation dose and leukaemia risk in patients treated for cancer of the cervix. J Natl Cancer Inst 79: 1295-1311

35. Hall P, Mattsson A, Boice JD, Jr. (1996) Thyroid cancer after diagnostic administration iodine-131. Radiat Res 145: 86-92

36. Muirhead CR, Goodill AA, Haylock RG, Vokes J, Little MP, Jackson DA, O'Hagan JA, Thomas JM, Kendall GM, Silk TJ, Bingham D, Berridge GL (1999) Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers [see comments]. J Radiol Prot 19: 3-26

37. BEIR-V. Committee on the Biological Effects of Ionizing Radiations. Health effects of exposure to low levels of ionizing radiation. BEIR V. Washington, D.C.: Natl. Acad. Press; 1990.

38. Darby SC (1991) Contribution of natural ionizing radiation to cancer mortality in the United States. In: (Brugge J) Brugge J.Brugge Js.| Book Title. Publisher, |:Edition ed| City, Pages|

39. Court Brown WM, Doll R, Spiers FW, Duffy BJ, McHugh MJ (1960) Geographical variation in leukaemia mortality in relation to background radiation and other factors. Br. Med. J. 1: 1753-1759

40. Allwright SPA, Colgan PA, McAulay IR, Mullins E (1983) Natural background radiation and cancer mortality in the Republic of Ireland. Int. J. Epidemiol. 12: 414-418

41. Muirhead CR, Butland BK, Green BM, Draper GJ (1991) Childhood leukaemia and natural radiation. Letter. Lancet 337: 503-504

42. Richardson S, Monfort C, Green M, Draper G, Muirhead C (1995) Spatial variation of natural radiation and childhood leukaemia incidence in Great Britain. Stat. Med. 14: 2487-2501

43. Chen D, Wei L (1991) Chromosome aberration, cancer mortality and hormetic phenomena among inhabitants in areas of high background radiation in China. J. Radiat. Res. (Tokyo) 32 Suppl. 2: 46-53

44. Tao Z, Wei L (1986) An epidemiological investigation of mutational diseases in the high background radiation area of Yangjiang, China. J. Radiat. Res. (Tokyo) 27: 141-150

45. Wei L, Zha Y, Tao Z, He W, Chen D, Yuan Y (1990) Epidemiological investigation of radiological effects in high background radiation areas of Yangjiang, China. J. Radiat. Res. (Tokyo) 31: 119-136

46. Wei L-x, Wang J-z (1994) Estimate of cancer risk for a large population continuously exposed to higher background radiation in Yangjiang, China. Chinese Med J 107: 541-544

47. Mason TJ, Miller RW (1974) Cosmic radiation at high altitudes and U.S. cancer mortality, 1950-1969. Radiat. Res. 60: 302-306

48. Weinberg CR, Brown KG (1987) Altitude, radiation, and mortality from cancer and heart disease. Radiat. Res. 112: 381-390

49. Yoshimoto Y, Delongchamp R, Mabuchi K (1994) In-utero exposed atomic bomb survivors: cancer risk update. Letter. Lancet 344: 345-346

50. Delongchamp RR, Mabuchi K, Yoshimoto Y, Preston DL (1997) Cancer mortality among atomic bomb survivors exposed in utero or as young children. Radiat Res 147: 385-395

51. Stewart A, Webb J, Giles D, Hewitt D (1956) Preliminary communication: malignant disease in childhood and diagnostic irradiation in utero. Lancet Sept 1: 447-448

52. Bithell JF, Stiller, C.A. (1988) A new calculation of the carcinogenic risk of obstetric x-raying. Stat Med 7: 857-864

53. Oppenheim BE, Griem ML, Meier P (1975) The effects of diagnostic X-ray exposure on the human fetus: an examination of the evidence. Radiology 114: 529-34

54. MacMahon B (1962) Prenatal x-ray exposure and childhood cancer. J Natl Cancer Inst 28: 1173-1191

55. Muirhead CR, Kneale GW (1989) Prenatal irradiation and childhood cancer. J Radiol Prot 9: 209-212

56. Mole RH (1990) Childhood cancer after prenatal exposure to diagnostic X-ray examinations in Britain. Br J Cancer 62: 152-168

57. Salonen T, Saxen L (1975) Risk indicators in childhood malignancies. Int J Cancer 15: 941-6

58. Akleyev AV, Lyubchansky ER (1994) Environmental and medical effects of nuclear weapon production on the Southern Urals. Sci Total Envir 142: 1-8

59. Degteva MO, Kozheurov VP, Tolstykh EI, Vorobiova MI, Anspaugh LR, Napier BA, Kovtun AN (2000) The Techa River dosimetry system: methods for the reconstruction of internal dose. Health Phys 79: 24-35

60. Degteva MO, Vorobiova MI, Kozheurov VP, Tolstykh EI, Anspaugh LR, Napier BA (2000) Dose reconstruction system for the exposed population living along the Techa River. Health Phys 78: 542-54

Table 1

Approaches to assessing upper limits of low-LET low dose and low dose rates for determing risks of cancer induction in humans [1]

Basis of estimation	Low dose (mGy)	Low dose rate (mGy min^{-1})
Based mainly on epidemiological data		
UNSCEAR 1986 [6]	200	0.05
UNSCEAR 1993 [7]	200	0.1
Physiological and animal data		
Linear term dominant in parametric fits to single-cell dose response	20-40	-
Microdosimetric evaluation of minimal multi-track coincidences in cell nucleus	0.2	10^{-8} (lifetime)
Observed dose-rate effects in animal carcinogenesis	-	0.06

Table 2

Thyroid cancer risks in patents receiving diagnostic amounts of 131-I (Hall, unpublished data)

Number of patients	Observed number of cases	Standardised incidence ratio	95% Confidence interval
All patients			
36,443	124	3.11	2.56 – 3.65
Referred under the suspicion of a thyroid tumour			
10,856	64	4.89	3.69 – 6.08
Previous external radiotherapy			
1,792	25	14.20	8.64 – 19.77
Referred for other reasons			
23,795	35	1.40	0.94 – 1.86

Table 3

Thyroid cancer incidence rates in children under 15 years of age at diagnosis in Belarus, Russian Federation, and Ukraine [1]

Country / region	Number of cases per 100,000 children											
	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Belarus	0.2	0.3	0.4	0.3	1.9	3.9	3.9	5.5	5.1	5.6	4.8	5.6
Russian Federation, Bryansk Region	0	0.3	0	0	0.3	0.3	0.9	0.3	2.8	2.5	0.6	2.2
Ukraine	0.2	0.1	0.1	0.1	0.2	0.2	0.5	0.4	0.5	0.6	0.4	0.5

Table 4

Factors that complicate calculation of radiation risk, especially at low doses

Factor	Comment
Dose	Cell killing at high doses, apoptosis, repair or carcinogenesis at lower doses
Dose rate	Probably higher risk at brief exposure, time for repair at protracted exposure
Gender	Somewhat higher risks for women
Age	Somewhat higher risks for those exposed as young, dependant on type of tumour
Latency	Varies with time
Smoking	Interacts with ionizing radiation
Medical treatments	Chemotherapy induces leukaemia
Outcome	Cancer incidence and mortality may differ
Background rates	Radiation risk varies with background rates
Tumour tissue	Differ in susceptibility
Molecular factors	Extent of molecular repair at low doses is not known, the effect of inherited genomic instability is not known.

CLUSTERS OF LEUKAEMIA AMONG YOUNG PEOPLE LIVING NEAR NUCLEAR SITES, WITH A FOCUS ON STUDIES PERFORMED IN THE NORD-COTENTIN (France)

Dominique LAURIER

Institute for Protection and Nuclear Safety, Human Health Protection and Dosimetry Division, Risk Assessment and Management Department, Laboratory of Epidemiology and Health Detriment Analysis, IPSN, DPHD/SEGR/LEADS, France

SUMMARY

The question of leukaemia clusters around nuclear installations has been a matter of concern since 1983. This article presents a brief overview of the state of the art, and then focuses on the example of the excess of leukaemia suggested near the French nuclear fuel reprocessing plant located in La Hague.

A large number of studies in the world have evaluated the existence of an increased risk of leukaemia among young people living near nuclear plants. A few clusters of leukaemia have been confirmed near certain nuclear sites (at least, for the nuclear fuel reprocessing plants at Sellafield and Dounreay). Nonetheless, no increase in the frequency of leukaemia is observed in general among young people living near nuclear sites, and localised excesses of leukaemia have also been identified far from any nuclear site. Although analytic studies set up to search for the causes of such excesses near nuclear sites have resulted in the rejection of some hypotheses (environmental exposure to radiation, preconceptional paternal exposure), they have been so far unable to provide a definitive explanation for the clusters observed.

An excess of leukaemia cases among young people living in the vicinity of the La Hague reprocessing plant has been suggested in 1995. The hypothesis of a link between the risk of leukaemia and environmental exposure to radiation was proposed by the same researchers two years latter, on the basis of the results of a case-control study. The existence of an excess of leukaemia cases has not been confirmed by a subsequent follow-up of incidence. The radioecological study that has been performed in response to the controversy concluded that exposure due to discharges from local nuclear installations was unlikely to be implicated to any salient degree in the elevated incidence of leukaemia observed in the La Hague surroundings, nor could explain the associations observed in the case-control study between the risk of leukaemia and specific behaviours.

A scientific controversy and an important media coverage followed the suggestion of the cluster, and made it difficult to communicate results. One reason was the insufficiency of leukaemia registries in France. This system has developed since then and will provide a more general framework to put in perspective such putative localised excess. Also, some elements can be proposed from the experience of the Nord-Cotentin Radioecology Group to help the credibility of the results and the communication toward the population.

INTRODUCTION

The first cluster of leukaemia has been observed in 1983 among children living near the Sellafield nuclear fuel reprocessing plant (Great Britain). Since then, many epidemiological studies set out to analyse the risk of leukaemia near nuclear sites, primarily among those younger than 25 years of age. Today, after 16 years of accumulated results, the existence of an increased risk of leukaemia among young people living near a nuclear site remains highly controversial.

In its first part, this article presents an overview of the state of the art regarding the frequency of leukaemia around nuclear installations in the world and the hypotheses proposed to explain the observed excesses. In its second part, it focuses on the excess of leukaemia cases suggested near the French reprocessing plant of La Hague, considering both epidemiologic, radioecologic and communication aspects of the performed studies.

CLUSTERS OF LEUKAEMIA AMONG YOUNG PEOPLE NEAR NUCLEAR SITES: THE STATE OF THE ART

Leukaemia among young people

Leukaemia is a rare disease: for those under 15 years of age, the incidence rates vary between 1.5 and 5.0 per 100 000, (1). Nearly 80 percent of these cases are acute leukaemia, for which the remission rate is now almost 75 percent (2). Morbidity is therefore a better indicator of the real frequency of childhood leukaemia in a population than mortality, but information about morbidity needs registries, i.e. a systematic and exhaustive recording of all new cases.

Today, very little is known about the aetiology of leukaemia among young people (3). Several epidemiological studies, in particular the follow-up of Hiroshima and Nagasaki survivors, have shown that leukaemia can be induced by ionizing radiation, especially among young people with a fairly short latency period after exposure (4, 5). Other recognised risk factors are consumption of some medications by the mother (e.g., chloramphenicol) and some congenital malformations (e.g., trisomy 21) (6). Other factors have been suggested, such as viral agents (7) or exposure to pesticides (8). Nonetheless, these factors concern only a small proportion of the cases, and most cases of leukaemia have no known cause.

Descriptive studies

Cluster studies search for an abnormally high concentration of cases in a given place, e.g. answering the question "Is the frequency of leukaemia near nuclear sites higher than it should be ?". Schematically, the methodology is always the same. It consists in cutting the study area into zones according to the distance to the nuclear site. In each zone, the number of observed cases during a given period is counted. The number of expected cases is obtained by multiplying the size of the resident population by reference rates (national rates or rates from a region dissociated with a nuclear site). An excess of risk can then be determined by comparing the observed number of cases with the expected one. Since then, many epidemiologic studies have set out to analyze the risk of cancer. Most studies of clusters near nuclear sites have considered leukemia globally, not

differentiating between subtypes (acute or chronic, lymphoblastic or myeloid). Non-Hodgkin's lymphoma, characterized by malignancies similar to leukemia in the lymphoid tissues, has also often been studied together with it. Cluster studies may concern a single area ("local" studies) or may analyse several sites simultaneously ("multi-site" studies).

Local studies

A large number of local cluster studies have been published since 1984 in many countries, but mainly in the U.K. and the United States (9). These studies were generally very small, concerning a few cases. Most of them show no excess of leukaemia among the young people living around these installations, or suggested excesses that were not confirmed by further studies. Nonetheless, three clusters were identified that are detailed below (Figure 1).

In November 1983, a British local TV station announced that a high number of leukaemia cases had occurred among the children living in Seascale, a village located three kilometres from the Sellafield nuclear fuel reprocessing plant (Great Britain). This cluster of leukaemia cases was confirmed one year later. Seven cases were recorded between 1955 and 1984 among those younger than 25 years of age living in the village of Seascale, where less than one case was expected (estimated relative risk greater than ten) (10). Subsequently, numerous studies have analysed the situation around Sellafield, and the cluster seems confined to the village of Seascale (11). The persistence of an excess over time has been confirmed during the 1984-1992 period (12).

In 1986, a second cluster in the same age group was reported in Scotland, near the nuclear reprocessing plant of Dounreay. It involved five cases observed between 1979 and 1984 within a radius of 12.5 km (compared to 0.5 expected cases). The estimated relative risk was close to ten, indicating a highly significant excess (13). The persistence of this cluster was confirmed through 1993, even if the relative risk tends to decrease with time (estimated relative risk of 2 on the period 1968-1993) (14).

More recently, another cluster was identified in Germany, close to the nuclear power station at Krümmel (Schleswig-Holstein). During 1990 and 1991, five children younger than 15 years living in the community of Elbmarsch located two kilometres from the plant were diagnosed with leukaemia, when only 0.12 cases were expected (estimated relative risk greater than 40) (15). Between 1994 and 1996, four new cases appeared in a 10-km radius around the plant, thereby suggesting that this excess is persisting over time (estimated relative risk of 3 on the period 1990-1996) (16).

Multi-site studies

As an outgrowth of these local studies, multi-site studies were launched, considering the risk of leukaemia around several nuclear sites simultaneously. Because these studies involve large numbers—from several dozen to several thousand cases—their statistical power is better than that of local studies. The results can thus be interpreted within a larger, more general, framework.

Most of these studies were performed in England (17, 18). The largest study so far conducted in this field concerned 4100 leukaemia cases among children aged 0 to 14 years around 29 nuclear sites in all of England (11). Other multi-sites studies were performed in Scotland (14), in the United States (19), in Canada (Ontario) (20), in France (mortality studies) (21, 22), in Germany (23, 24), in Japan (mortality study) (25), in Sweden (26) and in Spain (mortality study) (27). The general conclusion that can be

drawn from these studies is that the probability of leukaemia clusters is not higher near the nuclear sites than elsewhere or than expected.

Three multi-site studies in England and in Germany also considered the frequency of leukaemia among young people near "potential" sites, that is, sites envisaged for the construction of a nuclear installation or non nuclear power plants (11, 23, 28). In all these studies, the risk of juvenile leukaemia around these sites was nearly similar to that observed around active nuclear sites. Other studies have observed a frequency of mortality from leukaemia similar before and after start-up at the sites under study (29).

Other relevant studies

In some countries, national registries exist that allow to analyse the geographical distribution of leukaemia cases. Statistically significant excesses of leukaemia incidence among children have also been observed in areas where there was no nuclear site and no specific source was suggested, for example in Scotland in Cambuslang (30) or in Germany in the village of Sittensen (31).

Discussion

Cluster studies constitute a crude epidemiological approach and present to some biases and limitations:

- They are based on counts of cases, and no individual information is available,

- Monitoring of the migration of subjects is not possible, and cases are considered indiscriminately of whether they have inhabited the area since birth or have relocated in the area only a few months previously,

- Local studies generally concern small numbers, observed in small zones. The results are therefore very sensitive to random fluctuations in the spatial and temporal distribution of observed cases and depend upon the period and the limits and numbers of zones chosen (32),

- With only a few exceptions, studies do not take into account any information about the exposure levels in the various zones,

- Some uncertainty exists concerning the estimation of the number of expected cases, because of uncertainties in the calculation of the size of the resident population or because of some variability in reference rates, which is almost never considered in the calculation of risk,

- As cluster research mostly takes place near nuclear sites, this may lead to overestimating the number of clusters in these areas. Furthermore, some studies have been performed specifically in response to an announcement of an excess.

These problems, concerning both the analytic methodology and the interpretation of results (33), bring the value of cluster studies into question (34). Certain authors even consider that these studies are "at best useless" (35). In response, some authors and organisations have drafted recommendations and procedural guidelines for performing or interpreting cluster studies (36). To limit the possibility of erroneous conclusions, a suggestion is that monitoring around a site should be continued after any cluster is observed, to verify the persistence of the excess. A second solution is to adopt new

methods to reduce some of the defects of these studies. Methodological research on this matter can almost be said to have boomed (37, 38).

Search for factors associated with leukaemia clusters

Beginning in the 1990's, analytic studies have searched for factors that might explain the observed excesses of leukaemia. Three principal hypotheses have been explored: environmental exposure to ionizing radiation, paternal preconceptional exposure, and an infectious cause.

Environmental exposure to ionizing radiation

Case-control studies have examined some behaviours that might lead to increased radiation exposure or contamination (39-42). A few, as recreational use of beaches (40, 42) and consumption of local fish and seafood (42) appeared as significant risk factors in some studies. But the factors studied can only be considered remote indicators of environmental exposure (to radioisotopes or to other toxic substances). A conclusion on the basis of such data that a link exists between the risk of leukaemia and environmental contamination calls for considerable caution as well as an estimate of the dose that might be ascribed to these activities.

Radioecologic studies have been performed starting in 1984 in Great Britain (43-45). Their objective is to carry out a realistic reconstruction of the doses of _ionizing_ radiation received by the neighbouring population and to estimate the associated cancer risk. A thorough dose reconstruction for the area around Sellafield has been published in 1995 (12, 46). It took into account the various routes of contamination as well as all the possible sources of exposure. The population of young people between 0 and 24 years who had lived in Seascale between 1945 and 1992 was reconstructed. Within that population, 81 percent of the estimated collective dose to the bone marrow was attributable to natural radioactivity, 11 percent to other sources (medical, Chernobyl and weapons fallout), and roughly eight percent to releases from the Sellafield plant (routine discharges and accidental releases). The number of expected cases attributable to radiation exposure was calculated at 0.46 and 0.04, respectively, for all sources of exposure and for releases from the Sellafield plant (compared with the 12 cases actually recorded in Seascale between 1955 and 1992). Overall, these radioecologic evaluations have shown that, in view of current knowledge about the relation between exposure to radiation and the risk of leukaemia, these dose levels are incompatible with the excess risks observed around some nuclear sites.

The overall available information indicates that the hypothesis of a causal role of environmental exposure to radioactivity cannot explain leukaemia clusters among young people near nuclear installations (12, 47).

Paternal preconceptional exposure

The hypothesis of a genetically transmitted disease was advanced in 1990 by M. Gardner _et al_. to explain the Sellafield cluster (39). In their case-control study, the authors observed that the risk of leukaemia among children of fathers having cumulated a dose greater than 100 mSv before conception was eight times higher than among other children. Several studies then tried to verify the existence of this relation. The overall results have invalidated this hypothesis (48, 49).

Infectious agent

The hypothesis of an infectious aetiology was proposed long ago for some types of leukaemia (7). To explain the existence of concentrations of childhood leukaemia cases near some nuclear installations, L. Kinlen has hypothesised viral transmission favoured by high rates of population mixing that occurs during the construction of these large industrial plants (50). Nevertheless, no such unknown virus has as yet been detected in any child with leukaemia. An alternative hypothesis supposes that acute lymphoid leukaemia might be a rare response to common infection among subjects with untrained immune system (51).

Some studies showing that leukaemia cases tend to cluster naturally in time and space (52-54) or suggesting seasonality in the occurrence of leukaemia (55) indirectly support this hypothesis. Some results from L. Kinlen show an increase in leukaemia incidence among children younger than 15 years old associated with the construction of industrial sites in rural regions of Great Britain, and suggest that this hypothesis could partly explain leukaemia clusters observed near the Sellafield and Dounreay reprocessing plants (56, 57). More recently, a new study in all Cumbria (the county including the Sellafield installation) confirmed an association between population mixing and the risk of leukaemia before 15 years of age, on the basis of geographical data but also on the basis of individual data (58). The model derived by the authors predicted more than half of the number of leukaemia cases actually recorded in the village of Seascale during the same period. These new results lead Sir R. Doll to state in his editorial that "…time may now have come when Kinlen's hypothesis of population mixing as a cause of childhood lymphatic leukaemia can be regarded as established" (59).

Discussion

The studies performed to research possible explanations to the observed clusters of leukaemia cases around nuclear sites have important limitations:

- The case-controls studies are generally based on very low numbers of subjects and are limited by the memory of the parents concerning past behaviours and consumption habits of their children,

- Radioecologic studies rely on many assumptions and many uncertainties exist in the dose estimations, which are generally difficult to quantify. Furthermore, the applicability of risk models to such low levels of chronic exposure is uncertain,

- Current knowledge indicates that preconceptional paternal irradiation could not account for a childhood leukaemia cluster by itself. But new laboratory results suggest that it may potentially provide a secondary environmental induction of malignancy (60). Research is ongoing on this issue,

- Most of the studies supporting the infectious hypothesis are geographical studies, which are associated to well documented biases. To date however, no laboratory experimental support has appeared, and the underlying agent or mechanism still remains unidentified.

It appears that the understanding of the causes of leukaemia clusters should more rely on large scale studies, such as the case-controls studies that have been launched in the US, the UK or in Germany (61-63).

Conclusion

Cluster studies show that an excess of leukaemia exists near some nuclear sites (at least, for the reprocessing plants at Sellafield and Dounreay). Nonetheless, the results of the multi-site studies invalidate the hypothesis whereby the frequency of leukaemia generally increases among young people living near nuclear sites. Moreover, excesses of leukaemia have also been identified far from any nuclear site.

Although analytic studies set up to search for the causes of such excesses near nuclear sites have resulted in the rejection of some hypotheses, they have been so far unable to provide a definitive explanation for the clusters observed. The development of research on individual sensitivity, exposure or effect biomarkers may in the future provide more sensitive tools that may also prove useful for epidemiological purposes.

THE LA HAGUE CLUSTER OF LEUKAEMIA CASE AND ITS CONTROVERSY

Reminder of the history (figure 2)

Nord-Cotentin is a region in the north-west of France, where four nuclear facilities are located (figure 3): the Navy Yard at Cherbourg, the nuclear fuel reprocessing plant at La Hague, the shallow land disposal repository facility at La Hague and the nuclear power plant at Flamanville.

In 1995, J.F. Viel *et al* published the results of a study of the incidence of leukaemia among persons aged 0-24 years living in Nord-Cotentin. The conclusion suggested an excess of leukaemia cases in the canton of Beaumont-Hague (an administrative unit corresponding approximately to a 10-km zone, where the La Hague reprocessing plant is located) (64). In January 1997, the same researchers published the results of a case-control study, the conclusion of which suggested a link between environmental exposure to radiation and the risk of leukaemia among the young people of Nord-Cotentin (42). The publication of these two studies aroused a heated debate, locally and nationally.

Accordingly, the French Ministry of Environment and the Secretariat for Health and Social Welfare decided to commission "a new epidemiological study in the Nord-Cotentin region". The committee, headed by Ch. Souleau, Professor of Pharmacy, included two working groups on epidemiology and radioecology. Because of internal conflicts, the committee stopped after submitting an intermediate report in July 1997 (65).

Two new missions were then decided by the French government in August 1997. The objective of the first one, headed by A. Spira, Professor of Public Health, was to analyse the epidemiological evidence in more depth, and to conduct some reflection on the surveillance of health risks in relation to exposure to *ionizing* radiation in France (66). The second mission (Nord-Cotentin Radioecology Group, GRNC), headed by A. Sugier, director for Protection at the Institute for Protection and Nuclear Safety, was to carry out a radioecological analysis in the Nord-Cotentin (67).

Descriptive studies of leukaemia frequency in the La Hague surroundings

Between 1989 and 1995, four studies examined the mortality from leukaemia among those younger than 25 years of age, near the La Hague reprocessing plant: no excess mortality from leukaemia was observed near the plant (21, 22, 68, 69).

In 1993, an incidence study was performed among those aged 0 to 24 years living within 35 km around the site. The area was broken down into three zones with radii of 10, 20 and 35 km (Figure 3). Leukaemia cases were searched for retrospectively for the period from 1978 through 1990. The total number of cases was 23, among which three were located in the canton of Beaumont-Hague. Neither an excess of risk near the plant nor a gradient of risk with the distance was observed (70). Two years later, the same researchers updated this study with a follow-up continued through 1992. This study did not show an excess number of leukaemia cases for the entire zone but did suggest an excess in the canton of Beaumont-Hague, which was on the borderline of statistical significance (4 cases observed compared with 1.4 expected, leading to an estimated relative risk of 2.8) (64).

Since 1993, the cancer registry in the region of La Manche allows to extend prospectively the monitoring of leukaemia incidence in the Nord-Cotentin area. No new case was reported for the 1993-96 period in the 10-km zone (71), and the authors concluded that there was no significant increase of leukaemia incidence among young people in the Nord-Cotentin (66).

Figure 4 presents the results of the three incidence studies cited above regarding the risk of leukaemia among young people in the canton of Beaumont-Hague. The results do not appear very different, even if they led to different interpretations. None of the risk estimations reach statistical significance, and the confidence interval are always large, due to the small number of observed cases. A new situation extended up to 1998 should be published soon by the registry of La Manche.

Analytic studies of childhood leukaemia risk performed in the Nord-Cotentin

The case-control study

In 1997, the results of a case-control study by D. Pobel and J.F. Viel were published, that attempted to determine the factors associated with the risk of leukaemia among the young people of Nord-Cotentin. This study included 27 cases and 192 controls, and considered more than 170 risk factors. Several factors were significantly associated with an increased risk of leukaemia: recreational use of local beaches by the children ($p<0.01$) or by their mothers during pregnancy ($p<0.01$) and frequency of consumption of local fish and shellfish by the children ($p<0.01$). The authors concluded that their results provided "some convincing evidence in childhood leukaemia of a causal role for environmental radiation exposure from recreational activity on beaches" (42).

This study received many critics, mainly from epidemiologists who pointed out its limits (small size, potential bias…) (72) and the important gap between the obtained results and the conclusions drawn by the authors (73, 74).

The radioecological study

In 1997, the GRNC began a radioecological analysis. Its principal objective was to estimate the local population exposure to *ionizing* radiation and deduce the expected associated risk of leukaemia. The Group brought together more than 50 experts from diverse organisations: inspectors, governmental experts, operators, experts from non governmental laboratories and foreign experts. The general approach, implicating four specialised working groups, is presented in figure 5. The exposure reconstruction was as complete and realistic as possible, considering all sources of *ionizing* radiation for all possible exposure pathways (external exposure, inhalation, ingestion). To provide results that could be directly interpretable, the study focused on the same population as the one considered by epidemiological studies: young people aged 0 to 24 years, residing in the canton of Beaumont-Hague between 1978 and 1996.

The estimated collective dose due to the discharges from the local nuclear facilities delivered to the red bone marrow (the pertinent organ for leukaemia risk) was less than 0.2% of the total exposure to *ionizing* radiation (including natural and medical sources and fallout from atmospheric nuclear arms testing and the Chernobyl accident). The number of cases of radiation-induced leukaemia attributable to discharges from the local nuclear facilities was less than 0.002. This estimate is very low in comparison to the 4 cases of leukaemia observed among the same population over the same period. It was thus concluded that exposure attributable to local nuclear facilities was unlikely to be involved to any salient degree in the elevated incidence of leukaemia observed in this region among young people. Furthermore, exposure scenarios were constructed to assess the increase in individual dose and risk associated with behaviours noted in the case-control study of D. Pobel and J.F. Viel (42); i.e. an intensive recreational beach use or an important consumption of local seafood. Exposure due to routine discharges from the local nuclear facilities associated with these scenarios did not notably increase the risk of radiation-induced leukaemia, and thus could not explain the associations observed in the case-control study (75).

The report of the GRNC was finalised in July 1999, after two years of work (67). The result constitutes the best estimate of the incidence of radiation-induced leukaemia attributable to environmental exposure to *ionizing* radiation among the young people living in the vicinity of the La Hague reprocessing plant, in the current state of knowledge. Nevertheless, this estimate must be interpreted in the light of the limitations inherent in the risk assessment process. In particular, the uncertainty around it has not been evaluated, which led some participants of the GRNC to express reservations about the interpretation of the result.

Ongoing studies

Following the recommendations of the Spira's report (66), several epidemiological studies have been proposed concerning the Nord-Cotentin region. The first one aimed at reconstructing precisely the movements of population that occurred locally between 1982 and 1991, which was a period of major constructions at the La Hague plant, and to evaluate the hypothesis of a link between population mixing and the risk of leukaemia. The results should be published in 2001. The second project is to perform a cohort study, including all young people that inhabited the canton of Beaumont Hague since 1978. This study is currently in its feasibility phase.

A continuation of the work of the GRNC has been commissioned by the French Ministries of Environment and Health in July 2000, with three new objectives: to quantify the uncertainty associated with the results of the radioecological study, to

confront the GRNC approach with that of the English COMARE (12), and to assess the impact of chemical discharges on the environment and on health in the Nord-Cotentin.

Management of the controversy and communication

Communicating results of cluster studies is sensitive because the announcement of a local excess of cancer cases always receives substantial media coverage (76). From the publication of the incidence study in 1995, but especially after the publication of the case-control study in 1997, a controversy developed, echoed by a large media coverage on a regional and national scale. The results published led to fears among the local population, enhanced by the following controversy. Faced with contradictory messages from nuclear operators, researchers or environmental associations, some women created in 1997 the "Angry Mothers" association to request for "information in which they could trust".

It was in this context that the French government commissioned Professor Ch. Souleau committee (65), which did not help to clarify the situation. The committee was composed of experts, mainly epidemiologists, including J.F. Viel the author of the studies. Critics developed inside the committee, insisting on the possible biases and the over-interpretation of the conclusions, such that JF Viel felt as victim of a "trial" and left the committee (77). Professor Ch. Souleau also decided to stop and sent a letter published by newspapers in which he attacked "the terrorism of Green parties and of environmental associations" (78).

Aware of these difficulties in communication, the GRNC adopted original rules of operation:

- Composition opened to representatives from French non governmental associations and to foreign radiation protection experts,

- Critical analysis at each step (review in depth of all data about discharges and environmental measurements, discussion of the parameters and of the internal mechanisms of transfer models,…),

- Unrestricted diffusion outside the GRNC of the documents produced during the course of work (meeting reports, progress reports,…),

- Free interpretation and communication for all GRNC members; no obligation to reach a final consensus but an effort to clarify the divergences.

These rules helped for the communication of and the public confidence in the results. Results were largely diffused toward three different public: the general population (through public meetings and newspapers), experts and authorities (through reports, CD-Roms, web site including all results (http://www.ipsn.fr/nord-cotentin/)) and the scientists (presentations to congresses, scientific publications (79, 80)). The message, that clearly mentioned the different appreciation of the results of the calculation and even the refusal from one member of the GRNC to approve the report, have been perceived as reassuring by the local population.

Development of health surveillance in France

Due to its low frequency, the distribution of leukaemia cases is highly variable in time and space (32). This fact makes it difficult to discuss the validity of a suggested localised

excess, based on a small number of cases, if no other source of information is available to put the excess in perspective.

Some countries possess national cancer registries (81). Since the 60's, numerous studies have looked at the distribution of leukaemia cases over time and in space (52, 82-86). In general, these studies take into account large areas and thus consider very large numbers, with sophisticated spatial statistical methods. A recent international study (EuroClus) included more than 13,000 cases (87). Most of these studies reached the conclusion that there is a tendency towards spatial clustering of juvenile leukaemia cases. In addition, the issue of leukaemia around nuclear sites is not the only problem using this type of investigation, and many other studies have also considered the spatial distribution of cancers near non-nuclear sites, such as industrial facilities (88) and radio transmitters (89). The increased use of this type of analysis has even led to the creation in Great Britain of a unit specialised in the analysis of spatial phenomena, the Small Area Health Statistics Unit (90).

In France, only regional registries existed at the time of the La Hague Study. They cover approximately 10% of the French population, and are sufficient to provide a mean estimate of cancer incidence in France (91). For the Nord-Cotentin region, the cancer registry of La Manche began its activity in 1994, and received agreement by the French National Committee of Registries in 1995. Even if the excess of leukaemia suggested in the canton of Beaumont-Hague is not statistically significant, the estimated relative risk of leukaemia is still between two and three, which justifies the prolongation of leukaemia incidence monitoring in this area. Nevertheless, the system is insufficient to inform on the spatial distribution of cases nation-wide. A national registry of childhood leukaemia has been created in 1995, and received agreement by the French National Committee of Registries in 1998 (92). The creation of this registry cannot be considered as a direct consequence of the La Hague cluster, but it will provide a general framework if a new excess of cases is identified in the future. A national registry for childhood cancers is in preparation. Other registries were recommended in the final report of the Spira's committee (thyroid cancer, brain cancer, multiple myelomas,…) (66), but the development of a surveillance of these pathologies is still under discussion.

An improvement of the surveillance of exposure to radiation in France was also recommended by both the Spira's committee and the GRNC (66, 67), to provide a better basis for estimation of exposures to the general population (modification of environmental monitoring in regards to the current regulatory approach, improvement of the knowledge of life habits,…).

Conclusion

The existence of an excess of leukaemia cases among young people in the vicinity of the La Hague reprocessing plant suggested in 1995 has not been confirmed. Follow-up of the incidence is still ongoing. The radioecological study performed in response to the controversy concluded that exposure due to discharges from local nuclear installations was unlikely to be involved at any salient degree in the elevated incidence of leukaemia observed in the region, nor could explain the associations observed in the case-control study between the risk of leukaemia and specific behaviours.

Concerning the La Hague cluster, one important element to reduce the controversy has been to replace the suggested excess in the frame of the current epidemiologic

knowledge. From this point of view, it could be interesting to take advantage of an international collaboration of researchers involved in the field.

One of the problems encountered at La Hague was the lack of other source of information to put the putative excess into perspective. A national registry now exists in France for childhood leukaemia, but registries should be recommended also for other pathologies. Such national cancer registries already exist in many European countries, and could provide a basis for new etiological hypotheses.

Nevertheless, even in countries with national surveillance of cancer morbidity, communication about clusters remain difficult. Regarding this point, the inclusion of experts from environmental associations in the GRNC has been an important element in the construction of the credibility in the final results. A plural composition for commissions, including operators, governmental and non-governmental experts, should be proposed to help the communication toward the general population.

REFERENCES

1. Parkin DM, Kramarova E, Draper GJ, et al. International incidence of childhood cancer, Vol II. IARC, France, Lyon, IARC Scientif. Pub. n°144, 1998.
2. Liesner RJ, Goldstone AH. ABC of clinical haematology: the acute leukaemias. BMJ 1997;314:733-736.
3. Ross JA, Davies SM, Potter JD, Robison LL. Epidemiology of childhood leukemia, with a focus on infants. Epidemiol. Rev. 1994;16:243-272.
4. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation, New York: United Nations, UNSCEAR 1994 Report to the General Assembly, with scientific annexes, 1994.
5. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br. J. Radiol. 1997;70:130-139.
6. Robison LL. Down syndrome and leukemia. Leukemia 1992;6:5-7.
7. Mueller N. Overview: viral agents and cancer. Environ. Health Perspect. 1995;103:259-61.
8. Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am. J. Epidemiol. 2000;151:639-46.
9. Laurier D, Bard D. Epidemiologic studies of leukemia among persons under 25 years of age living near nuclear sites. Epidemiol. Rev. 1999;21:188-206.
10. Black D. Investigation of the possible increased incidences of cancer in West Cumbria, London: HMSO, 1984.
11. Bithell JF, Dutton SJ, Draper GJ, Neary NM. Distribution of childhood leukaemias and non-Hodgkin's lymphomas near nuclear installations in England and Wales. BMJ 1994;309:501-505.
12. Committee on Medical Aspects of Radiation in the Environment. The incidence of cancer and leukaemia in young people in the vicinity of the Sellafield site, West Cumbria: Further studies and an update of the situation since the publication of the report of the Black Advisory Group in 1984, United Kingdom, London: Department of Health, COMARE IV, 1996.
13. Heasman MA, Kemp IW, Urquhart JD, Black R. Childhood leukaemia in northern Scotland. Lancet 1986;1:266.
14. Sharp L, Black RJ, Harkness EF, McKinney PA. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in the vicinity of nuclear sites in Scotland, 1968-93. Occup. Environ. Med. 1996;53:823-831.
15. Schmitz-Feuerhake I, Schroder H, Dannheim B, et al. Leukaemia near water nuclear reactor. Lancet 1993;342:1484.
16. Hoffmann W, Dieckmann H, Schmitz-Feuerhake I. A cluster of childhood leukemia near a nuclear reactor in northern Germany. Arch. Environ. Health 1997;52:275-280.
17. Cook-Mozaffari PJ, Darby SC, Doll R, et al. Geographical variation in mortality from leukaemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969-78. Br. J. Cancer 1989;59:476-485.
18. Goldsmith JR. Nuclear installations and childhood cancer in the UK: mortality and incidence for 0-9-year-old children, 1971-1980. Sci. Total Environ. 1992;127:13-35.
19. Jablon S, Hrubec Z, Boice JD, Jr. Cancer in populations living near nuclear facilities. A survey of mortality nationwide and incidence in two states. JAMA 1991;265:1403-1408.

20. McLaughlin JR, Clarke EA, Nishri ED, Anderson TW. Childhood leukemia in the vicinity of Canadian nuclear facilities. Cancer Causes Control 1993;4:51-58.
21. Hill C, Laplanche A. Mortalité par cancer autour d'installations nucléaires françaises entre 0 et 24 ans, France, Paris: INSERM/Douin, 1992.
22. Hattchouel JM, Laplanche A, Hill C. Leukaemia mortality around French nuclear sites. Br. J. Cancer 1995;71:651-3.
23. Michaelis J, Keller B, Haaf G, Kaatsch P. Incidence of childhood malignancies in the vicinity of west German nuclear power plants. Cancer Causes Control 1992;3:255-263.
24. Michaelis J. Recent epidemiological studies on ionizing radiation and childhood cancer in Germany. Int. J. Radiat. Biol. 1998;73:377-81.
25. Iwasaki T, Nishizawa K, Murata M. Leukaemia and lymphoma mortality in the vicinity of nuclear power stations in Japan, 1973-1987. J. Radiol. Protect. 1995;15:271-288.
26. Waller LA, Turnbull BW, Gustafsson G, Hjalmars U, Andersson B. Detection and assessment of clusters of disease: an application to nuclear power plant facilities and childhood leukaemia in Sweden. Stat. Med. 1995;14:3-16.
27. Lopez-Abente G, Aragones N, Pollan M, Ruiz M, Gandarillas A. Leukemia, lymphomas, and myeloma mortality in the vicinity of nuclear power plants and nuclear fuel facilities in Spain. Cancer Epidemiol. Biomarkers Prev. 1999;8:925-34.
28. Cook-Mozaffari P, Darby S, Doll R. Cancer near potential sites of nuclear installations. Lancet 1989;2:1145-1147.
29. Jablon S, Hrubec Z, Boice JD, Jr., Stone BJ. Cancer in populations living near nuclear facilities. Vol 2 - Individual facilities: cancer before and after start-up, Washington: National Cancer Institute, NIH Pub N°. 90-874-2, 1990.
30. Hole DJ, Lamont DW, Brogan RT, Gibson BE, Gray MM, Gillis CR. Concurrent childhood and adult excesses of leukaemia in geographical areas. Lancet 1994;343:1439-1440.
31. Grosche B. Leucémies infantiles dans le voisinage des centrales nucléaires en Allemagne. Symposium sur les agrégats de leucémie. Canada, Ottawa: Atomic Energy Control Board, 1992:19-25.
32. Valenty M, Laurier D. Distribution géographique de la mortalité par leucémie chez les 0-24 ans en France. Rev. Epidémiol. Santé Publ. 1997;45:527-30.
33. Urquhart JD. Studies of disease clustering: problems of interpretation. In: Elliot P, Cuzick J, English D, Stern R, eds. Geographical and environmental epidemiology: Methods for small-area studies. UK, Oxford: Oxford University Press, 1996:278-285.
34. Wartenberg D. Should we boost or bust cluster investigations? Epidemiology 1995;6:575-576.
35. Estève J. Quelles études épidémiologiques pour les personnes potentiellement exposées aux rayonnements ionisants ? Santé et Rayonnements Ionisants 1999;19:5-7.
36. Center for Disease Control. Guidelines for investigating clusters of health events. MMWR 1990;39:1-23.
37. Elliott P, Cuzick J, English D, Stern R. Geographical and environmental epidemiology: Methods for small-area studies, United Kingdom, Oxford: Oxford University Press, 1996.
38. Richardson S. Current developments in biostatistics. Rev. Epidémiol. Santé Publ. 1996;44:482-493.
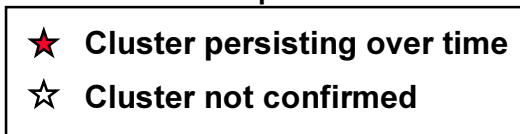
39. Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. BMJ 1990;300:423-429.

40. Urquhart JD, Black RJ, Muirhead MJ, et al. Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. BMJ 1991;302:687-692.

41. Roman E, Watson A, Beral V, et al. Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 years living in west Berkshire and north Hampshire health districts. BMJ 1993;306:615-621.

42. Pobel D, Viel JF. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited. BMJ 1997;314:101-106.

43. Stather JW, Wrixon AD, Simmonds JR. The risks of leukemia and other cancers in Seascale from radiation exposure. National Radiological Protection Board, United Kingdom, London: HMSO, NRPB-R177, 1984.

44. Dionan J, Muirhead CR, Wan SL, Wrixon AD. The risks of leukemia and other cancers in Thurso from radiation exposure. National Radiological Protection Board, United Kingdom, London: HMSO, NRPB-R196, 1986.

45. Dionan J, Wan SL, Wrixon AD. Radiation doses to members of the public around AWRE, Aldermaston, ROF, Burghfield and AERE, Harwell. National Radiological Protection Board, United Kingdom, London: HMSO, NRPB-R202, 1987.

46. Simmonds JR, Robinson CA, Philipps AW, Muirhead CR, Fry F. Risks of leukemia and other cancers in Seascale from all sources of ionizing radiation exposure. National Radiological Protection Board, United Kingdom, Chilton: HMSO, NRPB-R276, 1995.

47. Doll R. Epidemiological evidence of effects of small doses of ionizing radiation with a note on the causation of clusters of childhood leukaemia. J. Radiol. Protect. 1993;13:233-241.

48. Doll R, Evans HJ, Darby SC. Paternal exposure not to blame. Nature 1994;367:678-680.

49. Little MP, Charles MW, Wakeford R. A review of the risks of leukemia in relation to parental pre-conception exposure to radiation. Health Phys. 1995;68:299-310.

50. Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. Br. J. Cancer 1995;71:1-5.

51. Greaves MF. Aetiology of acute leukaemia. Lancet 1997;349:344-349.

52. Petridou E, Revinthi K, Alexander FE, et al. Space-time clustering of childhood leukaemia in Greece: evidence supporting a viral aetiology. Br. J. Cancer 1996;73:1278-1283.

53. Alexander FE, Boyle P, Carli PM, et al. Spatial temporal patterns in childhood leukaemia: further evidence for an infectious origin. EUROCLUS project. Br. J. Cancer 1998;77:812-7.

54. Birch JM, Alexander FE, Blair V, Eden OB, Taylor GM, McNally RJ. Space-time clustering patterns in childhood leukaemia support a role for infection. Br. J. Cancer 2000;82:1571-6.

55. Gilman EA, Sorahan T, Lancashire RJ, Lawrence GM, Cheng KK. Seasonality in the presentation of acute lymphoid leukaemia. Br. J. Cancer 1998;77:677-8.

56. Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. BMJ 1993;306:743-748.

57. Kinlen LJ, Dickson M, Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. BMJ 1995;310:763-768.

58. Dickinson HO, Parker L. Quantifying the effect of population mixing on childhood leukaemia risk: the Seascale cluster. Br. J. Cancer 1999;81:144-51.

59. Doll R. The Seascale cluster: a probable explanation. Br. J. Cancer 1999;81:3-5.

60. Lord BI. Transgenerational susceptibility to leukaemia induction resulting from preconception, paternal irradiation. Int. J. Radiat. Biol. 1999;75:801-10.

61. Robison LL, Buckley JD, Bunin G. Assessment of environmental and genetic factors in the etiology of childhood cancers: the Childrens Cancer Group epidemiology program. Environ. Health Perspect. 1995;103:111-116.

62. Meinert R, Kaletsch U, Kaatsch P, Schuz J, Michaelis J. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. Cancer Epidemiol. Biomarkers Prev. 1999;8:793-9.

63. U. K. Childhood Cancer Study Investigators. The United Kingdom Childhood Cancer Study: objectives, materials and methods. Br. J. Cancer 2000;82:1073-102.

64. Viel JF, Pobel D, Carre A. Incidence of leukaemia in young people around the La Hague nuclear waste reprocessing plant: a sensitivity analysis. Stat. Med. 1995;14:2459-2472.

65. Comité scientifique pour une nouvelle étude épidémiologique dans le Nord Cotentin. Rapport final du Comité scientifique : volets épidémiologique et radioécologique, France, Paris, 1997.

66. Spira A, Boutou O. Rayonnements ionisants et santé : mesure des expositions à la radioactivité et surveillance des effets sur la santé, France, Paris: La Documentation Française, 1999.

67. Nord-Cotentin Radioecology Group. Estimation of exposure levels to ionizing radiation and associated risks of leukemia for populations in the Nord-Cotentin: Synthesis, France, Fontenay-aux-Roses: Institute for Protection and Nuclear Safety, 2000.

68. Dousset M. Cancer mortality around La Hague nuclear facilities. Health Phys. 1989;56:875-884.

69. Viel JF, Richardson ST. Childhood leukaemia around the La Hague nuclear waste reprocessing plant. BMJ 1990;300:580-581.

70. Viel JF, Richardson S, Danel P, et al. Childhood leukemia incidence in the vicinity of La Hague nuclear-waste reprocessing facility (France). Cancer Causes Control 1993;4:341-343.

71. Guizard AV, Spira A, Troussard X, Collignon A, ARKM. Incidence des leucémies de 0 à 24 ans dans le Nord Cotentin. Rev. Épidémiol. Santé Publ. 1997;45:530-535.

72. Clavel J, Hemon D. Leukaemia near La Hague nuclear plant. Bias could have been introduced into study. BMJ. 1997;314:1553.

73. Law G, Roman E. Leukaemia near La Hague nuclear plant. Study design is questionable. BMJ 1997;314:1553.

74. Wakeford R. Leukaemia near La Hague nuclear plant. Scientific context is needed. BMJ 1997;314:1553-4.

75. Groupe Radioécologie Nord-Cotentin. Estimation des doses et des risques de leucémies associés (Volume 4), Fontenay-aux-Roses, Paris: Institut de Protection et de Sûreté Nucléaire, 1999.

76. Greenberg M, Wartenberg D. Understanding mass media coverage of disease clusters. Am. J. Epidemiol. 1990;132:S192-195.

77. Viel JF. La santé publique atomisée. Radioactivité et leucémies : les leçons de La Hague, France, Paris: Ed. La Découverte, 1998.

78. Estrades J, Remy E, Joly PB. L'expertise à la mesure des risques sanitaires : le cas des ESST et des leucémies du Nord-Cotentin. Programmes du CNRS : "Santé et Société : risques collectifs et situations de crise", Grenoble, Paris: INRA/ESR, 1999.

79. Laurier D, Rommens C, Drombry-Ringeard C, Merle-Szeremeta A, Degrange JP. Evaluation du risque de leucémie radio-induite à proximité d'installations nucléaires : l'étude radio-écologique Nord-Cotentin. Rev. Epidémiol. Santé Publ. 2000;48:2S24-2S36.

80. Rommens C, Laurier D, Sugier A. Methodology and results of the Nord-Cotentin radioecological study. J. Radiat. Protect. 2000:In Press.

81. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer incidence in five continents - Vol VII, France, Lyon: IARC, IARC Scientif. Pub. n°143, 1997.

82. Ederer F, Myers MH, Mantel N. A statistical problem in space and time: Do leukemia cases come in clusters? Biometrics 1964;20:626-638.

83. Openshaw S, Craft AW, Charlton M, Birch JM. Investigation of leukaemia clusters by use of a Geographical Analysis Machine. Lancet 1988;1:272-273.

84. Draper GJ. The geographical epidemiology of childhood leukaemia and non-Hodgkin lymphomas in Great Britain 1966-83, United Kingdom, London: HMSO, Studies on medical and population subjects N°53 OPCS, 1991.

85. Knox EG, Gilman E. Leukaemia clusters in Great Britain. 2. Geographical concentrations. J. Epidemiol. Community Health 1992;46:573-576.

86. Westermeier T, Michaelis J. Applicability of the Poisson distribution to model the data of the German Children's Cancer Registry. Radiat. Environ. Biophys. 1995;34:7-11.

87. Alexander FE, Boyle P, Carli PM, et al. Spatial clustering of childhood leukaemia: summary results from the EUROCLUS project. Br. J. Cancer 1998;77:818-24.

88. Wilkinson P, Thakrar B, Walls P, et al. Lymphohaematopoietic malignancy around all industrial complexes that include major oil refineries in Great Britain. Occup. Environ. Med. 1999;56:577-80.

89. Dolk H, Elliott P, Shaddick G, Walls P, Thakrar B. Cancer incidence near radio and television transmitters in Great Britain. II. All high power transmitters. Am. J. Epidemiol. 1997;145:10-17.

90. Elliott P, Westlake AJ, Hills M, et al. The Small Area Health Statistics Unit: a national facility for investigating health around point sources of environmental pollution in the United Kingdom. J. Epidemiol. Community Health 1992;46:345-349.

91. Ménegoz F, Chérié-Challine L. Le cancer en France : Incidence et Mortalité. Situation en 1995 et évolution entre 1975 et 1995. Ministère de l'emploi et de la solidarité, Réseau FRANCIM, Paris, France: La Documentation Française, 1998.

92. Chérié-Challine L, Lecomte P. Comité National des Registres. Rapport d'activité 1996-1999. Ministère de l'emploi et de la solidarité - INSERM - Institut de Veille Sanitaire, Paris, France: INSERM, 2000.

Figure 1 : Local cluster studies of leukaemia incidence among young people near nuclear installations in Europe
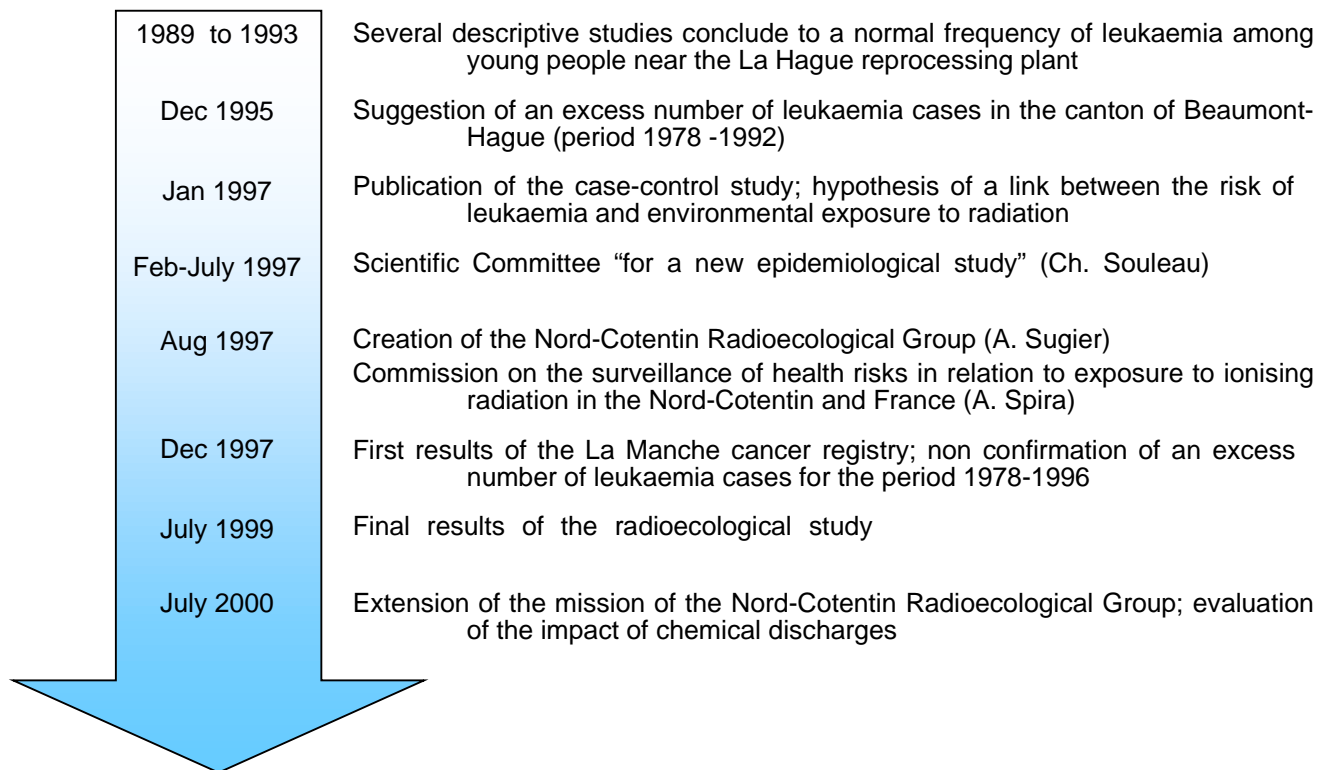
★ Cluster persisting over time

☆ Cluster not confirmed

1989 to 1993	Several descriptive studies conclude to a normal frequency of leukaemia among young people near the La Hague reprocessing plant
Dec 1995	Suggestion of an excess number of leukaemia cases in the canton of Beaumont-Hague (period 1978 -1992)
Jan 1997	Publication of the case-control study; hypothesis of a link between the risk of leukaemia and environmental exposure to radiation
Feb-July 1997	Scientific Committee "for a new epidemiological study" (Ch. Souleau)
Aug 1997	Creation of the Nord-Cotentin Radioecological Group (A. Sugier) Commission on the surveillance of health risks in relation to exposure to ionising radiation in the Nord-Cotentin and France (A. Spira)
Dec 1997	First results of the La Manche cancer registry; non confirmation of an excess number of leukaemia cases for the period 1978-1996
July 1999	Final results of the radioecological study
July 2000	Extension of the mission of the Nord-Cotentin Radioecological Group; evaluation of the impact of chemical discharges

Figure 2 : History of the studies conducted on the risk of leukaemia among young people in the canton of Beaumont Hague (Nord-Cotentin, France)

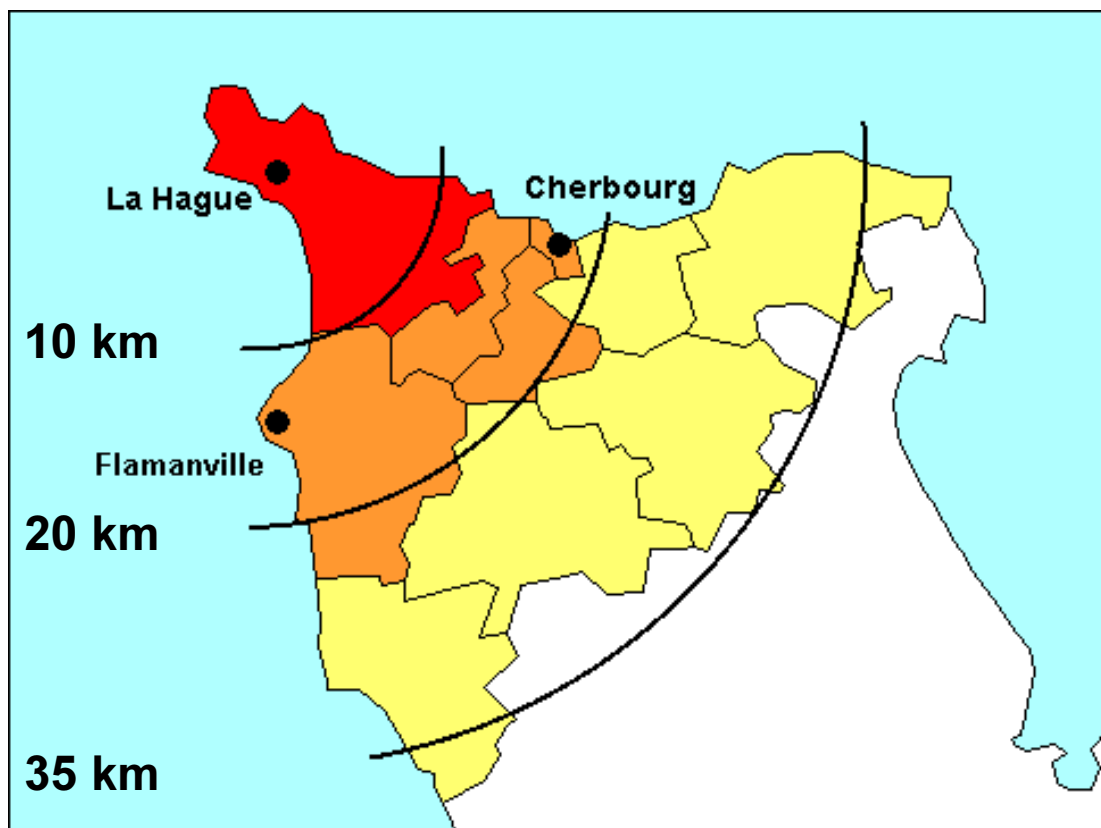**Figure 3 : Cluster study of leukaemia incidence in the Nord-Cotentin (France)**
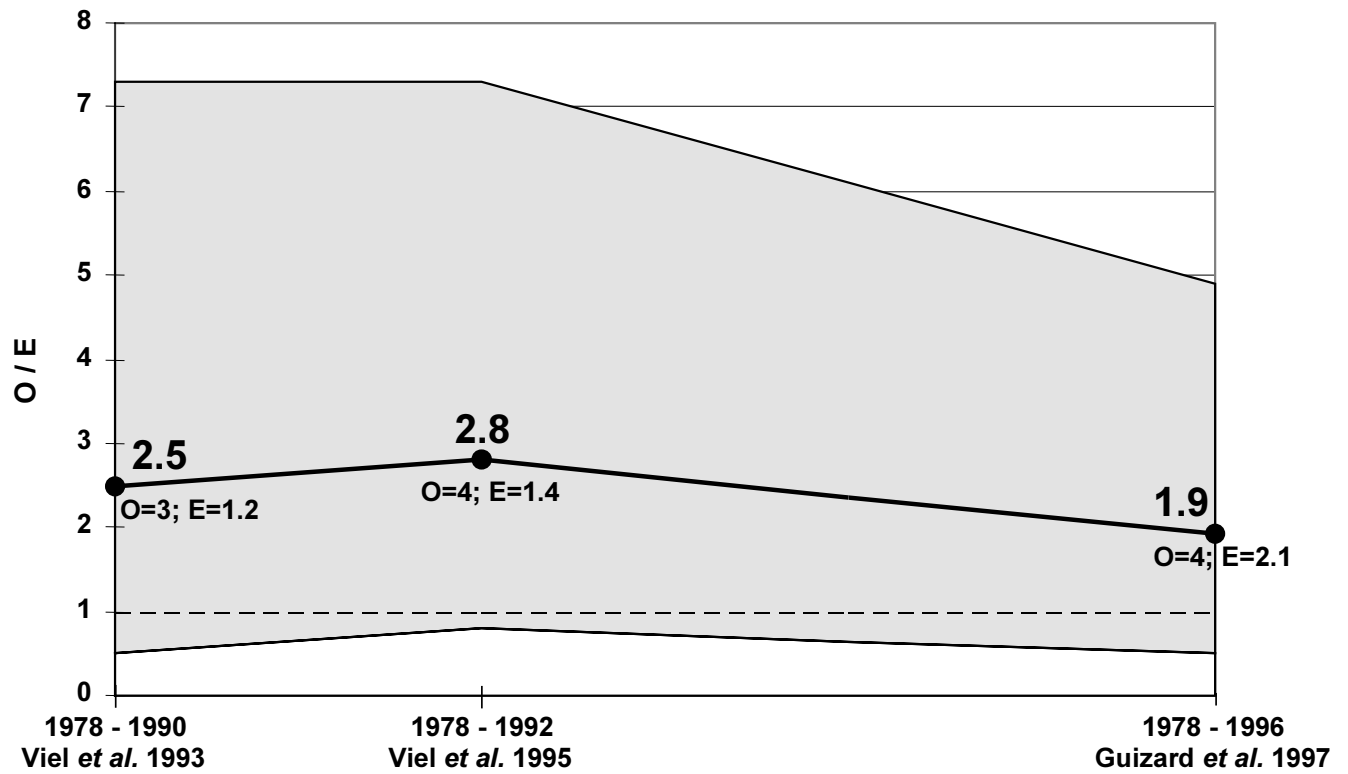
Figure 4 : Estimated relative risk* of leukaemia among young people residing in the canton of Beaumont-Hague (Nord-Cotentin, France)

O : number of observed cases   E : number of expected cases   95% Confidence Interval
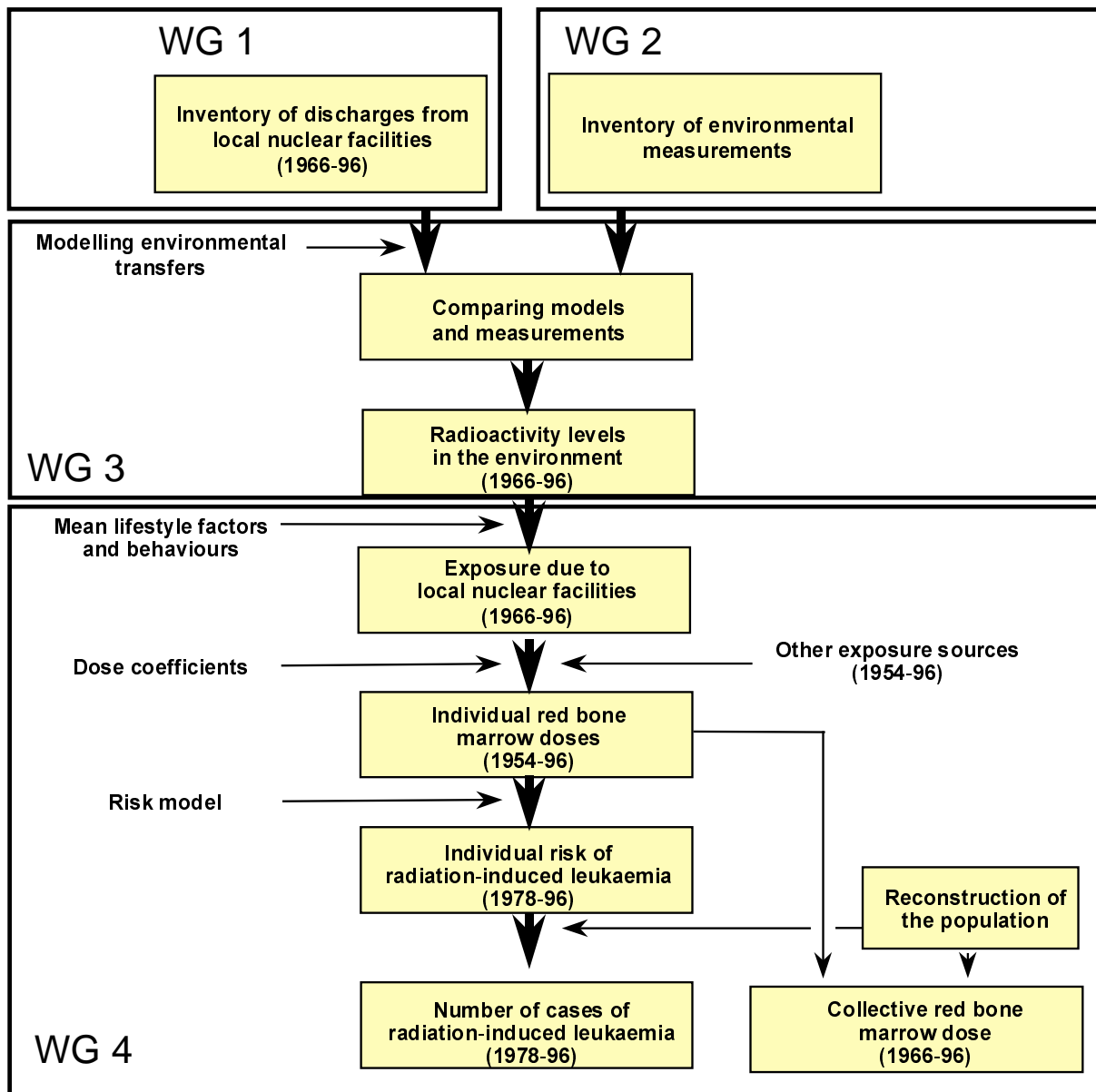* : O/E (Standardised Incidence Ratio)

Figure 5: Approach of the Nord-Cotentin Radioecology Group to assess the risk of radiation-induced leukaemia in the population of the canton of Beaumont-Hague (Nord-Cotentin, France)

WG : Working Group

Conclusions and Potential Implications

Dr C.R. MUIRHEAD

National Radiological Protection Board, United Kingdom

INTRODUCTION

This document presents the main conclusions and potential implications of the Scientific Seminar on Low Dose Ionizing Radiation and Cancer Risk, held in Luxembourg on 9 November 2000. While it is not intended to report in an exhaustive manner all of the opinions that were expressed by the speakers or by the audience, it takes account of the discussions that took place during the subsequent meeting of the "Article 31" Group of experts on 10 November 2000. The content of the document has been discussed within the RIHSS (Research Implications on Health Safety Standards) Working Party* and has been submitted for advice to the lecturers, whose remarks were taken into account as far as possible, subject sometimes to the final arbitration of the RIHSS Working Party.

1. RIHSS SEMINARS: RATIONALE

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

The approach adopted is the following: on the basis of input from the Directorate General Research of the European Commission and of information provided by individual members of the Article 31 Group of experts, each year the Working Party proposes relevant themes to the Article 31 Group that could be discussed during a subsequent seminar. After selection of the theme and approval of a draft programme by the Article 31 Group, the Working Party deals with the practical organization. The seminars involve invited speakers – mainly leading experts – who are asked to synthesize clearly the state-of-the-art in the field, with special attention paid to new information. Additional experts, identified by members of the Article 31 Group from their own country, take part in the seminars and act as peer reviewers. The Commission convenes the seminars on the day before a meeting of the Article 31 Group, in order that members of the Group can discuss the potential implications of the combined scientific results.

---

* The members of the RIHSS Working Party who contributed to the preparation of this document were the following members of the Article 31 Group: R Clarke, J Piechowski, P Smeesters (Chairman of the Working Party) and A Susanna. They were assisted by the following officials of the European Commission: V Ciani (DG Environment), Ms Sarro Vaquero (DG Environment) and D Teunen (DG Research).

2. BACKGROUND AND PURPOSE OF THE SEMINAR

There is substantial information from epidemiological studies on the effects of acute, high dose radiation exposure. In particular, studies of the Japanese atomic bomb survivors and of certain medically-exposed groups largely form the basis of existing radiation risk estimates, such as those developed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and by the International Commission on Radiological Protection (ICRP). However, some extrapolations are required when using the above epidemiological data to estimate cancer risks that are relevant for radiological protection. For example, risks at low exposures are currently extrapolated from findings at high doses, and from a limited period of follow-up to a full lifetime. In addition, there is interest in how cancer risks vary by the site of the cancer and by age at exposure.

An alternative method of assessing risks would be to use epidemiological studies of low dose populations. These studies encompass groups with occupational or environmental exposures, as well as A-bomb survivors and medically-exposed groups with low dose exposures. However, there are methodological limitations to some of these studies, which may restrict inferences concerning, for example, whether or not there is a threshold for radiation-induced cancer. Combining results from different studies may enhance statistical power, but – in so doing - care is needed in order to minimise the potential for misleading findings.

During the past two decades there have been various reports in different countries of raised rates of leukaemia among young people living near nuclear plants. Many of the early reports concerned installations in Britain, most notably the Sellafield reprocessing plant. More recently, there have been detailed investigations around the La Hague reprocessing plant in France. There are methodological issues associated with the interpretation of these cluster studies, such as what the distribution of leukaemias might be away from nuclear sites. Assessments of doses arising from radioactive releases from plants and from other sources can be helpful in this regard.

This seminar aimed to review the state-of-the-art on the above topics. In addition, the following questions were raised during the discussions:

- Is there a minimum dose/dose rate below which any epidemiological study on radiation-induced cancer inherently would have no statistical power?

- What is the natural distribution of leukaemia clusters in a population?

3. MAIN POINTS ARISING FROM THE PRESENTATIONS AND SUBSEQUENT DISCUSSION

3.1. UNSCEAR Lifetime Cancer Risk Estimates

The paper by **C Muirhead and D Preston** summarised the assessment of radiation-induced cancer risks made in the recent UNSCEAR 2000 report. The mortality estimates are based on the follow-up to the end of 1990 of 86,572 Japanese atomic bomb survivors. It has been estimated that about 420 out of the 7,827 cancer deaths observed up to that time among these survivors were due to radiation exposure from the bombings. Since

more than half of the survivors overall and over 85% of those exposed as children were still alive at the end of 1990, the future pattern of cancer risks will be important in determining lifetime cancer risks. UNSCEAR 2000 used two risk projection models for this purpose. Under the 'age-at-exposure' model (which is similar to a model used previously by UNSCEAR and ICRP), the relative risk of solid cancers is assumed to remain constant with time since exposure. Under the other model used by UNSCEAR (the 'attained-age' model), the relative risk varies with attained age and, for a given age at exposure, decreases with increasing time since exposure. Lifetime risk estimates based on the attained-age model are about 30% lower overall than those based on the age-at-exposure model. Furthermore, lifetime risks are higher for childhood exposures than for adult exposures under the latter model, but these risks are similar under the former model. At present, it is difficult to choose between these models based on the Japanese A-bomb data. The Group's view was that the age-at-exposure model continues to provide a reasonable fit to the observations, and therefore should be retained at present.

UNSCEAR's lifetime risk estimates for solid cancer mortality are based on the age-at-exposure model, namely about 9% for males, 13% for females and 11% averaged over sexes, following an acute dose of 1 Sv to a Japanese population. A different type of risk projection model was used for leukaemia, giving a lifetime risk estimate of about 1% for an acute dose of 1 Sv.

Analysis of the dose-response relationship in the A-bomb survivors provides information of the extrapolation of risks from high doses down to low doses. For leukaemia, this analysis points to a reduction by a factor of 2 in the risk per unit dose, when moving from high to low doses. For all solid cancers combined, the A-bomb data are generally consistent with a linear dose-response. The impact on these analyses of a likely under-estimation of neutron doses in Hiroshima is still unclear, although preliminary indications are that the effect may be small. Muirhead mentioned that the UNSCEAR 2000 report did not include a detailed review of the effects of both dose and dose rate on cancer risks. However, this topic was reviewed in the UNSCEAR 1993 report, where it was concluded that a reduction in the risk per unit dose of less than 3 was suggested for the extrapolation from high doses/high dose rates down to low doses/low dose rates. It was stated in the discussion that the Dose and Dose Rate Effectiveness Factor (DDREF) could vary according, for example, to the organ or to the radiation energy, although – for protection purposes – it would be best to use simple values.

The UNSCEAR 2000 report calculated risk factors for various cancer sites, based on the Japanese A-bomb data. Muirhead and Preston highlighted the differences that might arise in some of these values when they are transferred to other countries, for which the baseline rates differ from those in Japan (eg. for lung, breast and stomach cancer). UNSCEAR presented site-specific risk estimates for five countries, based both on relative and additive transfers of risks across populations. The tissue weighting factors recommended by ICRP fall within the ranges presented by UNSCEAR, although these ranges are wide in some instances, reflecting in part a lack of knowledge on the best way of transferring site-specific risks. However, the variation between countries in estimates for total cancer risk is less than that for individual cancer types.

In the discussion, it was pointed out that the ICRP tissue weighting factors had been developed for prospective protection. In contrast, when making a detailed assessment for a specific exposure scenario, information may be used that is more relevant to this scenario, eg. using a risk factor that might be age, sex and/or organ-specific. This includes estimating the probability that a given cancer has been induced by radiation,

setting emergency intervention levels (for iodine prophylaxis) and making individual risk estimates after partial body exposure (e.g. after some medical or accidental exposures). In specific situations such as these, the use of ICRP tissue weighting factors may not be appropriate.

The cancer risk estimates for acute high dose exposure made in UNSCEAR 2000 are consistent with those in earlier evaluations by UNSCEAR and ICRP. However, there may be around a factor of 2 uncertainty in these values for leukaemia and for solid cancers combined, which may be greater when looking at specific cancer sites, young ages at exposure and low doses. Strategies to reducing uncertainties include: continued follow-up of the A-bomb survivors and other high dose groups, dose-response analyses of updated data, and epidemiological studies of groups with low and/or protracted exposures.

3.2.   Low Dose Epidemiology

The paper by **P Hall** reviewed the epidemiological and statistical considerations that influence studies of populations exposed to low doses. Since epidemiological studies are observational rather than experimental in nature, they can be subject to bias (ie. systematic errors in the study design) or confounding (due to a factor that is correlated both with the exposure and disease under study). Examples of bias include: incomplete follow-up of a cohort of individuals – particularly if the level of follow-up varies by exposure (eg. owing to more intensive follow-up of exposed than non-exposed individuals); and failure to select a representative set of controls in a case-control study. Confounding might arise, for example, in a study of medical irradiation if the condition that gave rise to the exposure is related to the cancer risk; for example, through the use of radioiodine to investigate a suspected thyroid cancer. Correlation studies may be useful for generating hypotheses, but the lack of individual information on exposures and potential confounding factors implies that these studies are generally more limited than cohort or case-control studies. Bias and confounding could affect high dose studies as well as low dose studies. However, the impact on low dose studies is likely to be greater in general, because these studies are attempting to identify relatively small risks.

Statistical power can also limit inferences from low dose studies, including the size of the dose at which raised cancer risks might be seen. The statistical power of a study will generally increase with increasing values for the population size, length of follow-up and range of doses. It is sometimes possible to enhance statistical power by pooling data from different studies; for example, as has been performed with studies of thyroid cancer following external irradiation and with studies of cancer in radiation workers. However, some caveats are necessary:

- attention needs to be given to differences in the design of studies that are being pooled, since this might lead to erroneous findings;

- to this end, it is preferable to pool the original data from the various studies in a combined analysis, rather than pooling the published findings, as in a meta-analysis;

- it is important to allow for differences in baseline cancer rates (whether due to genetic or other factors) between the groups that are being pooled.

These approaches have been adopted both in the examples cited above and in an ongoing International Collaborative Study of Cancer Risk in Radiation Workers in the Nuclear Industry, coordinated by the International Agency for Research on Cancer.

The above considerations imply that not all low dose studies are informative. Amongst those that are, Hall drew attention to a recent analysis of the Japanese A-bomb data that showed a raised cancer risk for doses between 0 and 100 mSv, with an upper confidence limit for a dose threshold of 60 mSv. It was emphasised in the discussion that this does not mean that the data support a threshold of this magnitude, but rather that the data cannot exclude this possibility. In contrast, higher values for any threshold are inconsistent with the A-bomb data. This represents an advance from earlier assessments based on this study, which could not exclude values for a threshold below 100 mSv. Furthermore, the latest Japanese A-bomb data are consistent with a linear no-threshold hypothesis for cancer risks at low doses.

Amongst other informative low dose investigations, a combined analysis of studies of thyroid cancer following external radiation in childhood showed a dose-response consistent with linearity down to about 100 mSv. Furthermore, large studies on radiation workers and a combined analysis of such data point to an association between leukaemia risk and dose that is consistent with existing risk estimates. It was noted in the discussion that studies of occupational exposures provide information on exposures to doses that are not only low but also protracted, in contrast to the A-bomb study.

Data for emerging groups in the former Soviet Union, such as the population near the Techa River and workers at the Mayak nuclear facility in the Southern Urals, and clean-up workers at Chernobyl may provide further information in future, although some methodological aspects need to be resolved. In addition, mechanistic studies may give a better understanding of the effects of exposures to very low doses.

3.3. Leukaemia near Nuclear Installations

Leukaemia is a rare disease and, with the exception of ionizing radiation, little is known about the causes of the disease in young people. **D Laurier** reviewed cluster studies that have been performed in various countries, including the UK and Germany. Whilst raised levels of leukaemia in young people have been identified around some nuclear sites, studies around wider groupings of such sites have tended not to show increased risks. Furthermore, there have been some reports of raised leukaemia rates around potential sites for nuclear installations, although in general there have been fewer cluster investigations in areas away from nuclear installations than in their vicinity.

Inferences from cluster studies are limited owing to the methodology of this type of study. In contrast, case-control studies have allowed specific hypotheses to be tested, e.g. concerning environmental and paternal preconception radiation exposures. Case-control studies around nuclear sites have allowed some of these hypotheses to be rejected, but they do not provide an explanation for the clusters that have been seen. Radiological assessments performed around some sites (eg. Sellafield and Dounreay in the UK) also do not support a link with environmental radiation exposure. There has been some support for an infectious aetiology to leukaemia in young persons from geographical studies, but no agent has yet been identified.

A recent example that has received much attention, both scientifically and in the media, concerns the La Hague reprocessing plant in northern France. There had been indications

of a raised rate of leukaemia in young people living near La Hague, although this was not confirmed in a longer follow-up. A case-control study suggested an association between disease and environmental radiation exposure, but this result was based on a small number of cases and may have been due to bias. An assessment of radiation doses and associated leukaemia risks around La Hague did not indicate that radioactive releases from the site could explain either the claimed leukaemia excess or the findings of the case-control study.

Various issues arose in communicating the results of the research conducted in France, that are relevant to claimed clusters elsewhere. To perform the radiological assessment around La Hague, a committee was formed involving a wide range of experts, including those from operators, environmental organisations, government and non-governmental organisations. Even though the committee did not reach a consensus, the wide distribution of documents and findings helped build public confidence. During the meeting's discussion, examples were cited in which a study had been commissioned in order to address public concern, even though there was no strong prior scientific reason for expecting a raised cancer risk due to radiation in a certain locality.

The recent creation of a national registry of childhood leukaemia in France will help in putting the findings around nuclear installations in context. Some analyses of the general distribution of childhood leukaemia have been conducted in countries with existing national registries, and have shown a tendency for the disease to cluster spatially; for example, the international EUROCLUS project. It is difficult at present to state whether the findings around nuclear installations can be explained simply by statistical variations, variations in the baseline rate of the disease, and/or factors such as infections. However, work is continuing to address this topic.

4. CONCLUSIONS

The lifetime cancer risk estimates for acute high dose exposures made by UNSCEAR in its 2000 report agree well with those made by UNSCEAR and ICRP in previous evaluations; namely, a total fatal risk, averaged over sexes, of around 12% following an acute dose of 1 Sv. If a DDREF of 2 were applied to this value, the associated fatal risk factor would be close to the value of 5% per Sv at low doses and low dose rates recommended by ICRP Publication 60. Whilst risk estimates in the new UNSCEAR report are consistent with previous values, there are several sources of variability and uncertainty in these estimates:

- As in previous evaluations, UNSCEAR 2000 used a risk model under which the relative risk of solid cancers remains constant over time, but decreases with increasing age at exposure. This model implies that lifetime fatal cancer risks are about a factor 2 higher for exposure in childhood than for adult exposures. However, UNSCEAR also considered another risk projection model, under which the relative risk varies with attained age. In this case, lifetime risks are similar for child and adult exposures. At present, it is difficult to choose between these models based on the Japanese A-bomb data. However, for radiation protection purposes, greater emphasis may be placed on the age-at-exposure model, which provides a reasonable fit to the observations and which forms the basis of the latest UNSCEAR risk estimates. Continued follow-up of the A-bomb survivors should improve lifetime risk estimates.

- UNSCEAR 2000 examined cancer risks for specific organs. The ranges of values given by UNSCEAR are consistent with the tissue weighting factors recommended by ICRP. However, there is still uncertainty about the best method for transferring organ-specific cancer risks from the Japanese A-bomb survivors to populations in other countries with differing baseline rates. It should be recognised that the ICRP tissue weighting factors were designed for protection purposes. Consequently, when making detailed assessments, including individual risk estimates after partial body exposures (e.g. after some medical or accidental exposures), it may be preferable to use the best judgement on organ-specific risks in that situation.

- The UNSCEAR 2000 report did not contain a detailed review of DDREF or of dose rate effects specifically. However, dose-response analyses for the A-bomb survivors and medically-exposed groups tend to show that the risk per unit dose either remains roughly constant or decreases when moving from high down to low doses. The ability of epidemiological studies to detect raised cancer risks at very low doses is constrained not only by limitations on statistical power but also by the potential for small biases or confounding, which can be important when attempting to identify small effects. The A-bomb survivor data appear now to be inconsistent with dose-thresholds above 60 mSv, and this value might decrease with longer follow-up of the survivors. Furthermore, these data are consistent with a linear no-threshold hypothesis for cancer risks at low doses. In addition, raised risks of childhood cancer have been associated with doses received *in utero* that averaged 10-20 mSv. However, epidemiological data alone will not be able to prove the absence of a small threshold. To this end, considerations of mechanisms of carcinogenesis will be important. Nevertheless, it should be possible to gain further information on the effects of protracted low dose exposures from large analyses of data on radiation workers and possibly from studies of groups in the former Soviet Union.

The recent investigations around the La Hague processing plant in France have illustrated the problems of interpreting cluster studies of childhood leukaemia. There have been relatively few studies conducted away from nuclear sites, so making it difficult to put the results around nuclear sites in context. National data have been collected and analysed in some countries, and have shown some tendency for childhood leukaemia to cluster spatially. The collection of such data more generally would help in interpreting reported clusters. Nevertheless, cluster investigations are limited, owing to the lack of information at the individual level, and other types of investigations may sometimes be required, e.g. case-control studies or radiological assessments. The recent French experience also has highlighted how good communication can help improve the credence given by the public to the findings of such research.

ABSTRACT

The Treaty establishing the European Atomic Energy Community requires the Community to establish basic standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation.

The version of the standards presently in force, adopted in 1996, is based on risk factors extrapolated to lower doses and dose rates from data on health effects of acute high dose exposure of man to ionizing radiation.

The subject of the validity of such extrapolation is dealt with in three complementary papers focussed on

➢ Unscear Lifetime Cancer Risk Estimates

➢ Cancer Risks after exposure to low doses of ionizing radiation – Contribution and lessons learnt from epidemiology

➢ Clusters of leukaemia among young people living near nuclear sites, with a focus on studies performed in the Nord-Cotentin (France)

The publication is completed by considerations on the conclusions that can be drawn from the seminar and on the potential implications of the informations presented on the developments of the European Union radiation protection legislation.

LIST OF PARTICIPANTS

Belgium

Mr. P. GOVAERTS
CEN/SCK
Research Unit
Boeretang 200
B-2400 MOL

Dr. Patrick SMEESTERS
Service de Protection contre les Radiations
Ionisantes
Ministère de la Santé Publique et de
l'Environnement
Rue Ravenstein 36
B-1000 BRUXELLES

Mr André WAMBERSIE
RBNT 54/69
Av. Hippocrate 54
B-1200 Brussels

Denmark

Dr. Harriet DIGE-PETERSEN
Dept. of Clinical Physiology and Nuclear
Medicine
Glostrup Hospital, Copenhagen
DK-2600 Glostrup

Mr. K. ULBAK
Statens Institut for Straalehygiejne
Knapholm 7
DK-2730 HERLEV

Germany

Ms Prof. M. BLETTNER
Universität Bielefeld
Postfach 100131
D-33501 Bielefeld

Prof. Dr. Günther DIETZE
Head of the Ionizing Radiation Division
Physikalisch-Technische Bundesanstalt
Bundesallee 100
D-38116 BRAUNSCHWEIG

Dr. H.H. LANDFERMANN
Bundesministerium für Umwelt, Naturschutz
und Reaktorsicherheit,
Referat RS II 2
Postfach 12 06 29

D-53175 BONN

Greece **Mr. Panagiotis DIMITRIOU**
Greek Atomic Energy Commission
P.O. Box 60092
GR-153 10 AGIA PARAKEVI

Spain **Mr. David CANCIO**
Head Radiological Environmental Impact
(CIEMAT)
Ministerio de Ciencia y Tecnología
Avda. Complutense, 22
E-28040 MADRID

Prof. Miguel Javier ORTEGA ARAMBURU
Universitat Politécnica de Catalunya
Institut de Tecniques Energétiques
Avda. Diagonal 647
E-08028 BARCELONA

Prof. Eliseo VAÑO
Professor of Medical Physics
Radiology Department
Medicine School
Complutense University
E-28040 MADRID

Dr. Gonzalo LÓPEZ-ABENTE
Area de Epidemiologia del Cancer
Centro Nacional de Epidemiologia
Sinesio Delgado 6,
E-28029 Madrid

France **Dr. J. PIECHOWSKI**
CEA/HC
31, rue de la Fédération
F-75752 PARIS CEDEX 15

Madame Margot TIRMARCHE
IPSN / DPHD
BP 6
F-92265 Fontenay-aux-Roses Cedex

Ireland **Dr. Shane ALLWRIGHT**
Dept. of Community Health
Trinity College Centre for Health Sciences
Adelaide and Meath Hospital
Tallaght
IRL-Dublin 24

Italy **Mr. Antonio SUSANNA**

70

A.N.P.A.
(National Environmental Protection Agency)
Via Vitaliano Brancati 48
I-00144 ROMA

Ing. Enrico SGRILLI
A.N.P.A.
(National Environmental Protection Agency)
Via Vitaliano Brancati 48
I-00144 ROMA

Luxembourg   **Mr. Carlo BACK**
Direction de la Santé
Villa Louvigny
Allée Marconi
L-2120 LUXEMBOURG

Mr. Nico HARPES
Division de la Radioprotection
Direction de la Santé
Villa Louvigny
Allée Marconi
L-2120 LUXEMBOURG

Mr. Michel FEIDER
Direction de la Santé
Villa Louvigny
Allée Marconi
L-2120 LUXEMBOURG

Mrs Alexandra SCHREINER
Division de la Radioprotection
Villa Louvigny
Allée Marconi
L-2120 Luxembourg

Mr. Ferid SHANNOUN
Division de la Radioprotection
Direction de la Santé
Villa Louvigny
Allée Marconi
L-2120 LUXEMBOURG

The Netherlands   **Dr. J.TH.M. JANSEN**
IRI
TU Delft
Mekelweg 15
NL - 2629 JB Delft

Mr. Jan VAN DER STEEN
NRG Arnhem

Utrechtseweg 310
NL-6812 AR ARNHEM

Dr. Ciska ZUUR
Ministry of Environment
DGM/SAS/SNV/645
P.O.Box 30945
NL-2500 GX THE HAGUE

Austria	**Dr. Josef ZECHNER** Federal Ministry of Social Affairs Department IX/7 Radetzkystr. 2 A-1031 VIENNA
Portugal	**Mr. António FERRO DE CARVALHO** Instituto Tecnológico e Nuclear Ministry of Science and Technology - ITN Estrada Nacional n°10, Apartado 21 P-2686 953 SACAVEM
	Mr. António ORTINS DE BETTENCOURT Casa da Quinta da Graciosa Alto dos Gaios P-2765-067 ESTORIL
	Dr. Maria Berta MARTINS Estrada de A-da-Maia, 38 – 4°Fte P-1500 Lisboa
Finland	**Mr. Heimo KAHLOS** STUK - Radiation and Nuclear Safety Authority Laippatie 4 FIN-00880 HELSINKI
	Dr. Päivi KURTTIO STUK - Radiation and Nuclear Safety Authority P.O. Box 14 FIN-00881 Helsinki
	Mr. Olli VILKAMO STUK - Radiation and Nuclear Safety Authority P.O.Box 14 FIN-00881 HELSINKI
Sweden	**Mrs. Gunilla HELLSTRÖM** Swedish Radiation Protection Institute S-17116 STOCKHOLM
	Mr. Bengt G. PETTERSSON Swedish Nuclear Power Inspectorate

S-106 58 STOCKHOLM

United Kingdom   **Dr. S.A. HARBISON**
Winnats
White Hill Road
Meopham
UK - Kent DA13 0NS (England)

Dr. L. Keith HARDING
City Hospital NHS Trust
Dudley Road
UK-BIRMINGHAM B18 7QH

Dr. Hilary WALKER
Department of Health
Skipton House
80 London Road
UK-LONDON SE1 6LW

European Commission   **Mr. S. KAISER**
DG Environment

Mr V. CIANI
DG Environment

Mr. A. JANSSENS
DG Environment

Mrs Mercedes SARRO-VAQUERO
DG Environment

Mrs Salla SAASTAMOINEN
DG Environment

Ms Angela DELFINO
DG Environment

Mr. Diederik TEUNEN
DG Research

Mr Celso OSIMANI
Joint Research Centre - Ispra (Varese)

Mr. Dietmar F.G. REHER
Joint Research Center - Geel

Mr A.J. GONZALEZ
International Atomic Energy Agency - Vienna

14

KH-39-01-918-EN-N

Environment themes

General

Water

Land

Air

Industry

Waste

Nature

Urban

Funding

Law

Economics

Assessment

Nuclear

Risks

Education

see our publications catalogue at:
http://europa.eu.int/comm/environment/pubs/home.htm