ISSN - 0250 -5010

ANNALEN VAN DE BELGISCHE VERENIGING VOOR STRALINGSBESCHERMING

Vol.34, n°2, 2009 3e trim. 2009

Driemaandelijkse periodiek
1050 Brussel 5

Périodique trimestriel
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Ce numéro contient les textes des exposés présentés lors de réunions organisées par l'Association belge de Radioprotection à Bruxelles les 20 février et 24 avril 2009.

Dit nummer bevat de teksten van de uiteenzettingen ter gelegenheid van vergaderingen van de Belgische Vereniging voor Stralingsbescherming in Brussel op 20 februari en 24 april 2008.

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ANNEX E OF UNSCEAR 2006 SOURCES-TO EFFECTS ASSESSMENT FOR RADON IN HOMES AND WORKPLACES

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February 2009

ABSTRACT

Levels of radon indoors vary widely both within countries and between countries, with geometric mean concentrations of radon in indoor air ranging from less than 10 Bq/m³ in the Middle East to more than 100 Bq/m³ in several European countries. The average dose from inhalation of radon gas and its short-lived decay products represents typically about half of the effective dose received by members of the public from all natural sources of ionizing radiation. Radon and its short-lived decay products are well established as lung carcinogens. The recent pooling of residential case-control studies in Europe, North America and China now provides a direct method for estimating the lung cancer risk. The excess relative risk from long-term residential exposure to radon at 100 Bq/m³ is established with reasonably good precision and is considered to be about 0.16 (after correction for uncertainties in exposure assessment) with about a three-fold factor of uncertainty higher or lower than that value. Because of the synergistic interaction between the effects of radon exposure and those of inhalation to tobacco smoke, smokers account for nearly 90% of the population-averaged risk from residential exposure to radon.

1. RADON EXPOSURE IN THE UNSCEAR 2008 REPORT

Before presenting in part 2 the highlights of annex E of the UNSCEAR 2006 report, I will show you some recent data on radon exposure from the UNSCEAR 2008 report to the General Assembly.
The UNSCEAR 2008 values for the worldwide average annual doses and ranges of exposure from natural sources are summarized in Table 1. The average values are the same as in the UNSCEAR 2000 report, while the typical ranges are rounded off to 1 mSv/year for cosmic radiation, ingestion and external terrestrial radiation and to 10 mSv/year for exposure to radon (and its short-lived decay products).

The total number of workers exposed to ionizing radiation is in the UNSCEAR 2008 report estimated to be about 22.8 million, of whom 13 million are exposed to natural sources of radiation and about 9.8 million to artificial sources. Medical workers comprise 75% of the workers exposed to artificial sources of radiation. The corresponding numbers in the UNSCEAR 2000 report were much lower: 11.8 million occupationally exposed workers, of whom 6.5 million exposed to natural sources and 4.6 million to artificial sources.

The extraction and processing of radioactive ores that contain significant levels of natural radionuclides accounts for the vast majority of occupationally exposed workers, and radon is the main source of radiation exposure in underground mines of all types. Table 2 summarizes the exposure to radon in mines and other workplaces.

Table 1. Population exposure to natural sources of ionizing radiation from the UNSCEAR 2008 report to the General Assembly.

Natural source of exposure	Average dose (worldwide) mSv/year	Typical range of individual doses mSv/year	Comments
Inhalation (radon)	1.26	0.2 – 10	Much higher in some dwellings
External terrestrial	0.48	0.3 – 1	Higher is some locations
Ingestion	0.29	0.2 – 1	
Cosmic radiation	0.39	0.3 – 1	Increases with altitude
Total	**2.4**	**1 - 13**	**Sizeable population groups receive 10 – 20 mSv/year**

Table 2. Exposure to radon in the workplace from the UNSCEAR 2008 report to the General Assembly.

Workplace	Number of workers (thousands)	Collective dose man Sv/year	Average effective dose mSv/year
Coal mines	6 900	16 560	2.4
Other mines*	4 600	13 800	3.0
Other workplaces	1 250	6 000	4.8
Weighted average			**2.9**

* Excluding uranium mines

The trends in average annual occupational effective doses of ionizing radiation are shown in table 3. A decreasing trend can be seen for all categories of exposure to artificial sources. However, the overall weighted average effective dose increased because of the higher estimate of the exposure to natural sources of radiation.

Table 3. Trends in average annual occupational effective doses from the UNSCEAR 2008 report to the General Assembly.

Source of exposure	1980 - 1984 mSv/year	1990 - 1994 mSv/year	2000 - 2002 mSv/year
Natural sources	…	1.8	2.9
Military activities	0.7	0.2	0.1
Nuclear fuel cycle	3.7	1.8	1.0
Medical uses	0.6	0.3	0.5
Industrial uses	1.4	0.5	0.3
Miscellaneous	0.3	0.1	0.1
Weighted average	**1.3**	**0.8**	**1.8**

2. ANNEX E OF THE UNSCEAR 2006 REPORT

The publication of annex E "Sources-to-effects assessment for radon in homes and workplaces", which is part of volume II of the UNSCEAR 2006 report, has been delayed because of insufficient resources at the UNSCEAR secretariat. The information presented here is based on an advanced draft document.

There is no time to discuss the 150 pages of the annex in detail, which is already (or will soon be) available at the UNSCEAR website: *http://www.unscear.org/unscear/en/publications.html*
In my presentation I will keep to the structure of the annex and present from each chapter one or more highlights.

2.1. Sources and levels of radon exposure

There is a wide range of average outdoor radon concentrations ranging from one Bq/m³, typical of isolated islands or coastal regions, to more than 100 Bq/m³, typical of sites with high radon exhalation. UNSCEAR 2006 confirms the worldwide average outdoor values of the UNSCEAR 2000 report:

- a typical outdoor level of radon of 10 Bq/m³ and
- an outdoor equilibrium factor of 0.6.

The equilibrium factor (F) is the ratio of the equilibrium equivalent radon concentration (EEC) to the radon concentration.
$F = EEC / C(^{222}Rn)$ where ^{222}Rn and EEC concentrations are in Bq/m³
The EEC is defined as the equivalent concentration of the decay products in equilibrium with the radon gas that yields the same potential alpha energy per unit volume as the existing mixture.
$EEC = 0.105\ C(^{218}Po) + 0.516\ C(^{214}Pb) + 0.379\ C(^{214}Bi)$ (concentrations in Bq/m³)

Pressure-driven flow of soil gas through cracks in the floor is the main mechanism for entry of radon in buildings with high radon levels. This arises because the air inside buildings is normally at a slightly lower pressure than outside.

Levels of radon indoors vary widely both within countries and between countries. The lowest and the highest reported country averages are:

- 9 Bq/m³ in Egypt
- 184 Bq/m³ in Montenegro

UNSCEAR 2006 confirms the validity of the worldwide average indoor values of the UNSCEAR 2000 report:

- a typical indoor level of radon of 40 Bq/m³ and
- an indoor equilibrium factor of 0.4.

Data on indoor radon levels in a number of western countries from the UNSCEAR 2006 report is summarized in table 4. The average radon concentration in Belgium is estimated at 48 Bq/m³, with a geometric mean of 38 Bq/m³. The radon levels in Belgium are of the same order of magnitude

as the levels found in other western countries. Lower levels are reported for coastal countries like Japan, the United Kingdom and the Netherlands; comparable levels for the United States, Germany, Denmark and France and higher levels for Sweden and Finland.

Table 4. Average concentrations of radon in indoor air in a number of western countries (UNSCEAR, 2006).

Country	Average radon concentration Bq/m³	Geometric mean Bq/m³	Maximum value Bq/m³
Belgium	**48**	**38**	**12 000**
Worldwide average	**40**	**30**	
Japan	16	13	310
United Kingdom	20	14	17 000
Netherlands	23	18	380
Canada	34	14	1 720
United States	46	25	
Germany	50	40	> 10 000
Denmark	59	39	1 200
France	62	41	4 690
Norway	73	40	50 000
Switzerland	75	41	10 000
Sweden	108	56	84 000
Finland	120	84	20 000

2.2. Dosimetry

The health risk associated with radon arises from the inhalation of the short-lived decay products and the resulting dose to the critical cells of the respiratory tract. There are two approaches possible for deriving the radon progeny dose conversion factor.

- The epidemiological approach, used by ICRP 65 (1993), is to derive the conversion factor from epidemiological studies using the ratio of the risk of lung cancer in miners to the overall risk of cancer in the atomic bomb survivors and extrapolating the result to indoor conditions:
6 (nSv/h)/(Bq/m³).
- A non recommended approach using the ICRP 66 dosimetric model of the respiratory tract (1994) results in a 2.5 times higher dose conversion factor of 15 (nSv/h)/(Bq/m³).

As the most recent data published on the risks to underground miners suggests somewhat higher values (than the ones used in ICRP 65), UNSCEAR 2006 confirmed the 50% higher value used by the Committee in earlier evaluations of 9 (nSv/h)/(Bq/m³).

2.3. Experimental studies

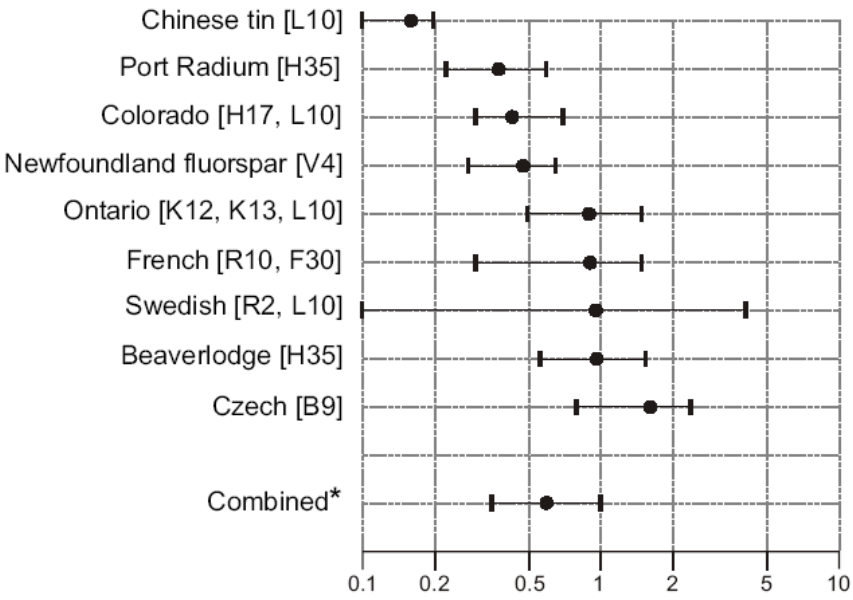
The animal studies support the observations from epidemiology that
- exposure to radon and its decay products is carcinogenic and that;
- the risks increase with increasing cumulative exposure, even for protracted exposures at low exposure rates.

Although several potential biomarkers of radon exposure have been studied, chromosomal aberrations still appear to be the most promising at this time, particularly due to the possible "signature" of high-LET exposures and the correlation with cancer risk.

2.4. Epidemiological studies of miners

Epidemiological studies of underground miners, by extrapolating the results down to levels of exposure seen in homes, until recently provided the main basis for estimating risks from residential exposure to radon and its short-lived decay products. UNSCEAR reviewed the epidemiological studies of miners with the main focus on the uncertainties in estimating past exposures. Important conclusions of this voluminous chapter are.
- All of the miner studies confirm the risk of lung cancer from exposure to radon decay products.
- Not all of the studies are of the same quality to estimate the dose-response relationship (number of excess lung cancers, quality of the exposure data and confounders such as smoking).

Figure 1 shows the estimated excess relative risk (ERR) of the various miner studies discussed in the UNSCEAR 2006 report. The ERR per 100 working level month (WLM) ranges over approximately a factor of 5.



* *Combined ERR per 100 WLM is 0.59 (95% confidence interval: 0.35, 1.0)*

Figure 1. Estimates of excess relative risk per 100 WLM from miner studies (UNSCEAR, 2006).

2.5. Epidemiological studies of residential exposures

The extrapolation of radon concentrations in the air in mines to those in homes provides an indirect basis for assessing the risks from residential exposure to radon. In addition, there are now more than twenty case-control studies of residential radon exposure and lung cancer. These studies typically assess the relative risk from exposure to radon on the basis of estimates of residential exposure over a period of 25 to 30 years prior to diagnosis of lung cancer.

Case-control studies use individual-related data, while ecological studies are based on data aggregated over geographical areas (average radon concentration and average lung cancer risk). This makes ecological studies vulnerable to biases not present in case-control studies like the correlations within each area between multiple risk factors. UNSCEAR questions on

that basis the relevance of ecological studies and in particular the large study of Cohen (1995) that generated a great deal of discussion over the past decade.

Cohen's ecological study is based on 275 000 measurements in all 50 US states showing decreasing (county average) lung cancer mortality rates in US counties with increasing (county average) radon exposure. Cohen's observation of a negative association between lung cancer and residential radon, as shown in figure 2, comes down to a protective effect of radon concentrations above 50 Bq/m³ relative to lower radon concentrations. The results from Cohen's study contrast markedly with the results from all cohort studies of radon-exposed miners and nearly all case-control studies of lung cancer and residential radon concentration. The main criticisms of Cohen's results have focused on the incomplete control for smoking, which is by far the most important cause of lung cancer.

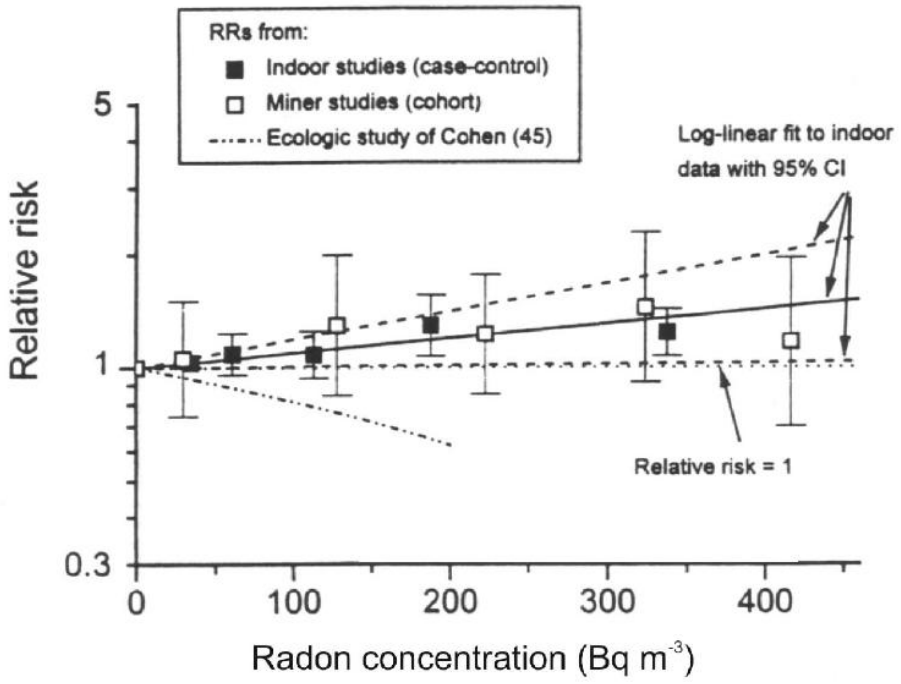


Figure 2. Risk estimates of lung cancer from exposure to radon (UNSCEAR 2006; adapted from Lubin, 1997). Shown are the summary relative risks from meta-analysis of eight indoor radon studies and from the pooled analysis of underground miner studies, restricted to exposures under 50 WLM, together with the estimated linear relative risk from the ecological study of Cohen (1995).

More than twenty case-control studies to estimate directly the risk of lung cancer associated with residential radon exposure have been published. Individually these studies have a limited statistical power, but pooled together they provide strong, direct evidence of risk from residential radon. Figure 3 shows the relative risks and 95% confidence intervals of the indoor case-control studies discussed in UNSCEAR 2006. Also shown at the bottom of figure 3 are the results of two meta-analyses, a pooled study in Germany and three pooled international studies in Europe (Darby, 2005), North America (Krewski, 2005) and China (Lubin, 2004).

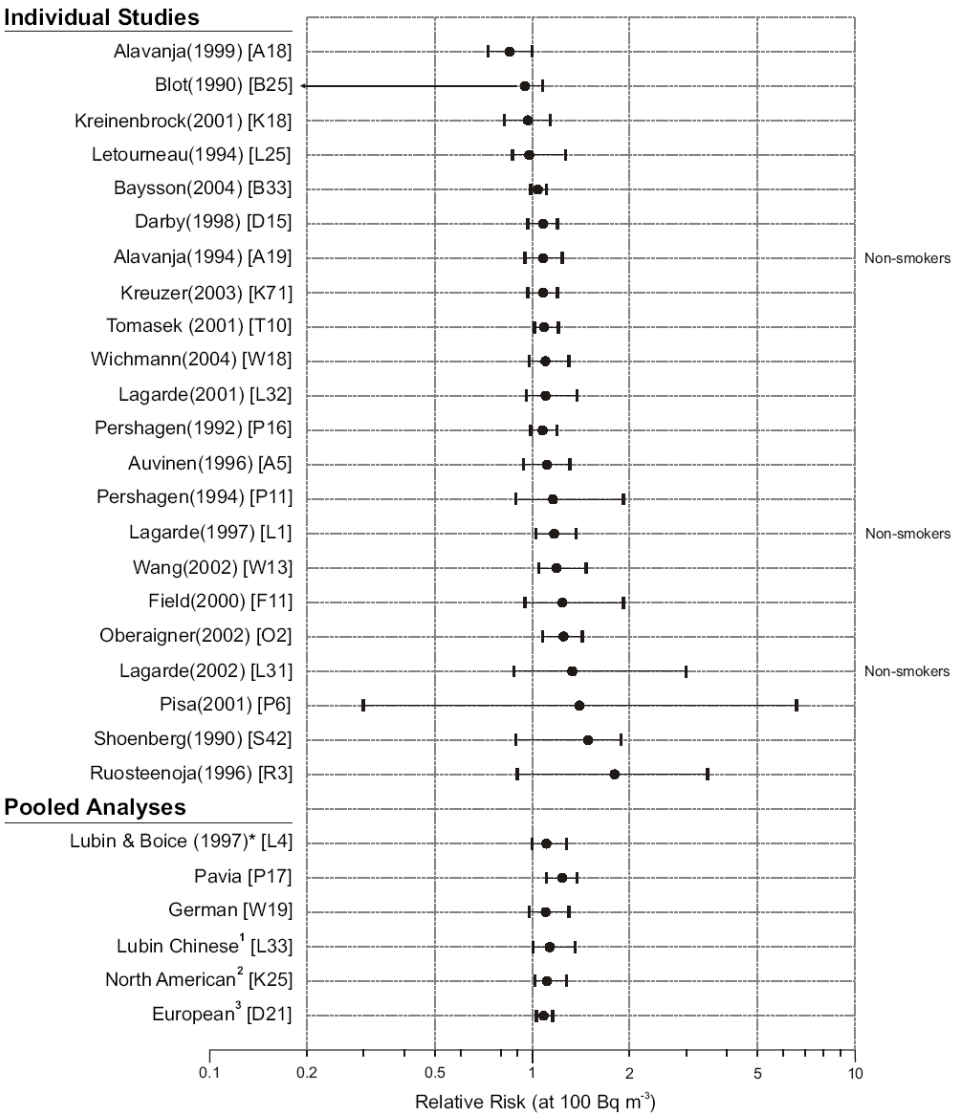


Figure 3. Relative risk estimates for exposure at 100 Bq/m³ from residential radon studies (UNSCEAR, 2006; from Baysson, 2004).

In the European study a collaborative analysis of individual data from 13 case-control studies was carried out including 7 148 people with lung cancer and 14 208 controls (Darby, 2005). The risk of lung cancer increased by 8.4% per 100 Bq/m³ increase in measured radon. This corresponds to an increase of 16% per 100 Bq/m³ after correction for the dilution caused by random uncertainties in measuring radon concentrations. In the absence of other causes of death, the absolute risks of lung cancer by age 75 years at radon concentrations of 0, 100 and 400 Bq/m³ would be about:

- lifelong non-smokers: 0,4%, 0.5% and 0.7%;
- cigarette smokers: 10%, 12% and 16%.

On the basis of the European pooled residential study, indoor radon would account for about 9% of deaths from lung cancer and about 2% of all deaths from cancer in Europe. For Belgium (48 Bq/m³) this comes down to 500 per year, from a total of 6 800 deaths from lung cancer per year.

The European pooled residential study (Darby, 2005) is in good agreement with the pooled North American (Krewski, 2005) and Chinese (Lubin, 2004) studies. As the European study has a better statistical power, UNSCEAR 2006 adopted the measurement corrected estimate of excess relative risk for developing lung cancer from the European pooled study of 0.16 per 100 Bq m^{-3}.

2.6. Effects of radon on organs and tissues other than lung

Under most circumstances, the largest dose from radon and its decay products will be that to the lung from inhalation of radon decay products. This is illustrated in table 5, adapted from UNSCEAR 2006 and Kendall 2002, showing annual doses at an indoor level of 200 Bq/m³. Doses to other organs are usually at least an order of magnitude smaller than doses to the lung. The calculated red bone marrow doses are not high enough to suggest that radon may be responsible for a proportion of childhood leukemias.

Table 5. Doses from inhaled radon decay products and radon at 200 Bq/m³ (UNSCEAR, 2006; from Kendall, 2002). The calculations use the default lung absorption to blood type M (moderate), an equilibrium factor between radon and decay products of 0.41 and 10% of the radon decay products not attached to aerosols.

Organ dose or committed effective dose	Radon decay products mSv/year	Radon gas mSv/year
Lung dose	159	1.2
Extrathoracic dose	70.9	
Red bone marrow dose	0.03	0.65
Kidney dose	0.54	0.05
Committed effective dose	19.7	0.28
Foetus dose	0.01	0.04
Skin dose	25	

Calculations indicate that decay products of radon deposited on the skin may be able to reach the sensitive basal cells where the skin is thin, for example on the face. An estimate of the skin dose from a year's exposure at 200 Bq/m³ is given in table 5. The sensitive basal cells are taken to be at depth of 50 μm, while the ranges of the 6.0 and 7.69 Mev α particles from ^{218}Po and ^{214}Po are about 47 and 70 μm.

Ingestion of water containing dissolved radon gas may be in some circumstances a significant exposure pathway. An important factor is how long the ingested water remains in the stomach. Table 6 presents the ingestion doses (Kendall, 2002) assuming an annual intake of 600 l of water containing 1000 Bq/l radon in equilibrium with its decay products. In contrast to the situation for inhalation, doses from ingestion of radon gas dominate those from ingestion of the decay products. A radon concentration of 1000 Bq/l in ingested water is a rather high value. It corresponds to the European Union recommended action level for radon in private wells (European Commission, 2001) and assumes no decrease for de-emanation before ingestion (for example as a result of boiling).

Table 6. Doses from radon decay products and from radon gas from ingesting water containing 1000 Bq/l assuming an annual water intake of 600 l (Kendall, 2002).

Organ dose or committed effective dose	Radon decay products mSv/year	Radon gas mSv/year
Lung dose	0.01	1.26
Stomach dose	1.15	50.4
Red bone marrow dose	0.03	0.66
Kidney dose	0.25	0.05
Committed effective dose	0.17	6.0
Foetus dose	0.01	0.05

Depending on the circumstances, a proportion of the radon dissolved in water will de-emanate when the water is used (showering, laundry, etc.). UNSCEAR 1993 recommended an average air-water concentration ratio of 10^{-4}. This means that radon in drinking water at 1000 Bq/l would give rise to radon in room air at about 0.1 Bq/l, i.e. 100 Bq/m³. Comparison of the doses in table 5 (scaled by a half) and those in table 6 shows an inhalation dose which exceeds that from ingestion.

2.7. Implications for risk assessment

UNSCEAR 2006 concludes that although there are major uncertainties in extrapolating the risks of exposure to radon from the studies of miners to assessing risks in the home, there is remarkably good agreement between the risk factors derived from studies of miners and those derived from residential case-control studies. Both the miner and the residential studies have advantages (+) and disadvantages (-); some of the more important are given below.

Miner studies

+ have the ability to examine factors that modify the simple linear dose effect relation (time since exposure, age at expose, exposure rate),

- have a high percentage of smokers and exposure to other pollutants.

Residential studies

+ have the advantage that the exposures were received at similar concentrations and conditions to those of interest.

- Individual residential studies have limited statistical power and meta-analysis suggested that the results of the studies were inconsistent.

2.8. Overall conclusions

UNSCEAR 2006 confirms the worldwide average values of the UNSCEAR 2000 report:

- a typical outdoor level and equilibrium factor of 10 Bq/m³ and 0.6;
- a typical indoor level and equilibrium factor of 40 Bq/m³ and 0.4.

UNSCEAR 2006 continues to recommend its long-established radon progeny dose conversion factor of 9 (nSv/h)/(Bq/m³).

UNSCEAR 2006 adopts the measurement corrected estimate of the European pooled study, 0.16 per 100 Bq/m³, as the current best available estimate of the risk from residential radon. Smokers account for nearly 90% of the population risk because of the synergistic interaction between radon exposure and smoking.

3. SUGGESTIONS ON THE DOSE CONVERSION FACTOR AND THE ACTION LEVEL IN DWELLINGS

I'll conclude my presentation on a personal note with two suggestions.

- The UNSCEAR 2006 conversion factor for the calculation of the population exposure is 50% higher than the ICRP 65 conversion convention (1993) for members of the public. I suggest stopping the current confusion by adopting the same (UNSCEAR) dose conversion factor for workers and members of the public. Anyhow, smoking, by the almost multiplicative relationship with radon, determines to a considerable extend the lung cancer risk.
- The European reference level (1991) for radon exposure in existing dwellings of 400 Bq/m³ corresponds to an excess lung cancer risk of 0.16 x 4 = 64%, although risk is observed at levels < 200 Bq/m³. I suggest lowering the European reference level for dwellings and for buildings with a high occupancy to 200 Bq/m³.

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Annales de l'Association belge de Radioprotection, Vol.34, n°2, 2009
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol.34, n°2, 2009

THE BYSTANDER EFFECT.

A NEED TO CHANGE THE RADIATION RISK ESTIMATION ?

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April 2009

Abstract

Recent studies have provided evidence of bystander effect. The bystander phenomenon has been tentatively linked to an elevated risk of health effect at low dose in human (cancer, congenital abnormalities, neurological disease and hereditary effects) but none of those health effects has so far been scientifically shown to be associated with such radiation-induced effects. The possibility cannot be excluded but remains purely speculative. Further investigations are needed to clarify the nature and the importance of the bystander effect for the risk estimation in the low dose range.

INTRODUCTION

There is no doubt about radiation biological effect at high doses. Such effects for which a clear dose-effect relationship exists are called deterministic effects.
At low dose, whatever the low dose received, if a cancer should appear, the severity of the effect is not questionable and it is the probability of having the effect which becomes of concern. Such effects are called probabilistic or stochastic. The **risk characterization** is the estimation of the incidence and

severity of the adverse effects likely to occur. The **risk estimation** consists of the quantification of that likelihood. In this purpose any low dose effect should be carefully evaluated.

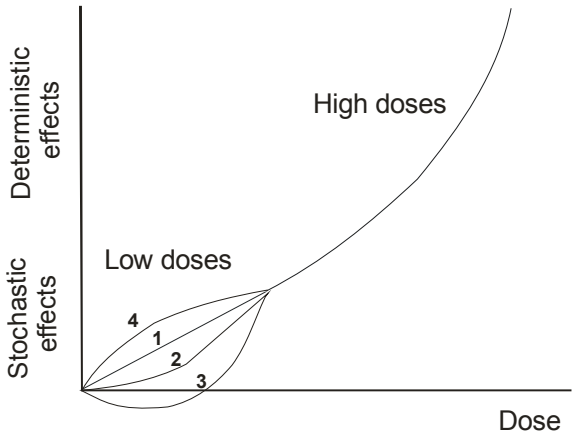
The problematic of studying the low dose effect resides in the statistical power of the studies. Indeed, the lower the doses, the lower the probability of a stochastic event such as chromosome aberration, mutation or cancer. The subsequent lack of evidence could indicate that either there is no harmful effect of radiation at such low levels of radiation or that the health effects, whatever they may be, are too few to be statistically significant.

To develop estimates of tumor frequencies at low radiation doses, it is necessary to extrapolate from responses at high dose. Different possibilities are to be considered: The choices generally are Linear Non Threshold, LNT (fig.«1»), non linear (fig.«2»), threshold (fig.«3») or greater than linear (fig.«4»). The Linear Non Threshold hypothesis estimates that the risk decreases when the dose decreases but the risk is never nil since a dose zero is impossible. (Natural radiation background). Non linear and threshold are respectively relevant for adaptive response and hormetic effect and would indicate that LNT is overestimating the risk. Greater than linear (fig.«4») indicates that LNT is underestimating the risk. The challenge in radiobiology is to establish which dose response curve shape best fits the tumor estimates at low doses.

Clearly any one of these three approaches has its own inherent sources of error and suppositions.

THE BYSTANDER EFFECT

The major concern in the low dose exposure range is the increased risk with increased radiation dose. The conventional approach is to consider that at low dose only some cells in our body are hit by the radiations, that their total number is dose dependent and that the probability or the risk to get



a cell transformed (a cancer cell) depends on the number of the cells being hit.
Recently several works (1, 3, 4, 6, 7, 8, 9, 11) have shown that at low doses, if effects are observed in radiation hit cells, effects also can appear in cells not directly hit by radiation but damaged by signal sent by neighboring cells. Such effects are referred to as untargeted effect or bystander effect.

Bystander effect would suggest that the target for radiation is larger than an individual hit cell and that a linear extrapolation of risks from high to low doses could underestimate the risk at low dose (fig.«4»).
Bystander effect has been demonstrated, especially after high-LET exposure, with various biological end points, chromatid exchange (5, 11), clonogenic survival (8, 10), micronucleus induction (13, 15), chromatin damage (14), chromosome aberrations (11) and apoptosis (4). A signal can be transferred by cell-to-cell communication or via the culture medium. The factors involved in the transmission of the effect have only partly been characterized. They may involve the diffusion of cytokines or long lived reactive oxygen species (ROS), the diffusion of paracrine proapoptotic or antiapoptotic factors induced by up-regulation of p.21. Bystander effect was reported to be suppressed by adaptive response induction.
Bystander effect is independent of dose. There is therefore no threshold. The lowest dose used to evidence a bystander effect *(single alpha particle track to one cell or low dose to a cell population)* caused the same amount of bystander end points as doses that were orders of magnitude higher. Bystander effects reported for γ-ray are with dose of 500mGy and above. For α-particles and other high-LET radiation used in bystander studies, the dose to the nucleus was calculated to be 130-500 mGy per particle traversal. The most critical question remains therefore whether the bystander effect exists for low-LET radiation dose <100 mGy.
Data from the literature show pronounced bystander effect in a variety of cell lines. Recently T. Groesser et al. (2) pointed a lack of bystander effect from high–LET radiation for early cytogenetic end points. These results were in contradiction with those of several published reports (7, 10, 14, 15, 16) but were confirmed by Mothersill who tested in her laboratory the same cells. However when changing the culture medium, a bystander effect appeared.

To reconcile such conflicting data it is suggested that the epigenetic status of the specific cell line used or the precise culture conditions and medium supplements such as serum could be critical for inducing bystander effect (2).
It has been proposed that the bystander response could be the initiating event in radiation-induced genomic instability (4). The instability induced by bystander effect is frequent and *nonclonal* but tumors do have *a clonal* origin. Bystander effect therefore does not appear to be directly involved in cellular transformation but, by the induced genomic instability, would favor its occurrence and increase the cancer incidence above the estimation provided by LNT hypothesis.

It is also important to note that the experimental results supporting the bystander effect involve only *in vitro* model systems. To evidence bystander effect in *in vivo* systems appears clearly not possible. Mancuso et al. (6) working on shielded cerebellum reported the first proof-of-principle that bystander effects are factual *in vivo* events with carcinogenic potential, and implicate the need for re-evaluation of approaches currently used to estimate radiation-associated health risks. We might however consider that such long distance bystander effects described by these author's are more likely related to the abscopal effect, a well known systemic effect for which the mechanisms might be totally different.

CONCLUSION

If bystander effect is important, we should consider that it has already operated in the population over many thousands of generations and is included in any low dose effect studies. Epidemiology should then clearly indicate that LNT underestimates the risk.
Epidemiological evidence however supports the LNT hypothesis. International epidemiological research on health effects of low doses of ionizing radiation has progressed in a classical way through dose estimations of exposed populations.
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the ICRP (International Commission Radiological Protection) and the US National Academy of Sciences (BEIR VII) reviewed the scientific progress worldwide and recently came to conclusions still supporting a linear non threshold hypothesis as best fit to assess and manage low level

exposure to ionizing radiation in the current context of uncertainty.
New investigations are needed to understand the mechanisms of bystander induction, the factors involved in the signal transmission, the role the bystander effect can play in vivo and verify if bystander effect is linked exclusively to ionizing radiation exposure or is a cell reaction to any stress. Only clear answer to those questions can allow to estimate the impact, if any, of bystander effect in the low dose radiation risk.

Acknowledgements
These studies were supported by the NOTE IP 036465 (FI6R), Euratom specific programme for research and training on nuclear energy, 6th FP of the EC.

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Oncogenic bystander radiation effects in Patched heterozygous mouse cerebellum.
PNAS **105**, 34, 12445–12450 (2008)

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16- H. Yang, V. Anzenberg and K.D. Held, The time dependence of bystander responses induced by iron-ion radiation in normal human skin fibroblasts. *Radiat. Res.* **168**, 292-298 (2007)

Highlights of the UNSCEAR 2006 Report

Annex C: Non-targeted and delayed effects of exposure to ionising radiation

Prof. Sisko Salomaa

STUK - Radiation and Nuclear Safety Authority, Finland
BVS-ABR meeting, 20.2.2006 Brussels

General remarks

- Vol II of 2006 Report (including Annex C) has not been published yet (Feb 2009)
- Summary of Annex C is available in Vol.I
- 578 references
- review of papers up to year 2005

Content of Annex C

Foreword

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

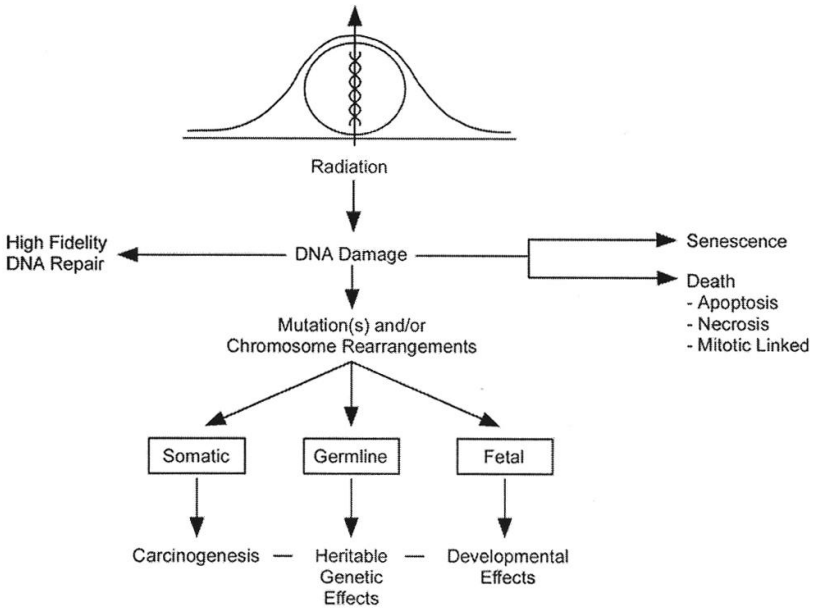


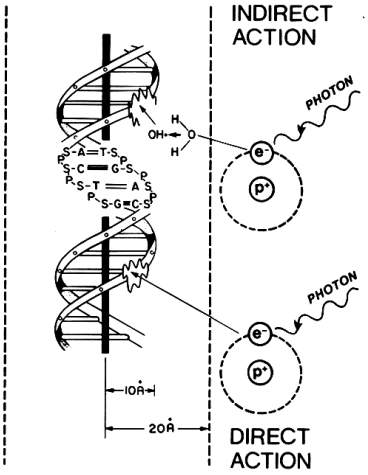
Figure I. The prevailing paradigm for the biological effects of cellular exposure to ionizing radiation.

Implicit in evaluating radiation effects is that the nucleus is the target, and that the deposition of energy induces the effect.

DNA damage is the result of direct and indirect effects of radiation

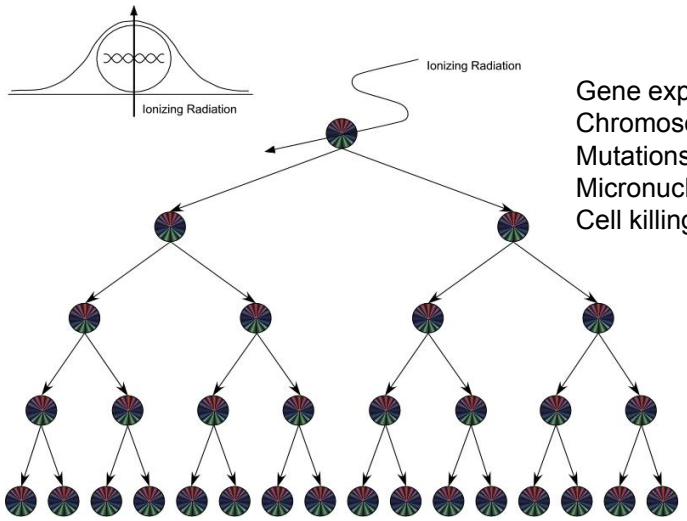
Damage / Gy of X-rays:

- 40 DSBs
- 150 DNA crosslinks
- 1,000 SSB
- 2,500 base damages



From: Hall, "Radiobiology for the Radiologist"

Conventional paradigm for radiation effects: Effects occur in "hit" (targeted) cells



In addition to these "targeted effects" the new biology reveals "non-targeted effects" of ionizing radiation

Induced genomic instability: observed in the progeny of an irradiated cell that may / may not have been subject to energy deposition events

Bystander effects: occur in cells that were not traversed by radiation and are induced by signals from irradiated cells

Implications for radiation protection?

I. Radiation-induced genomic instability

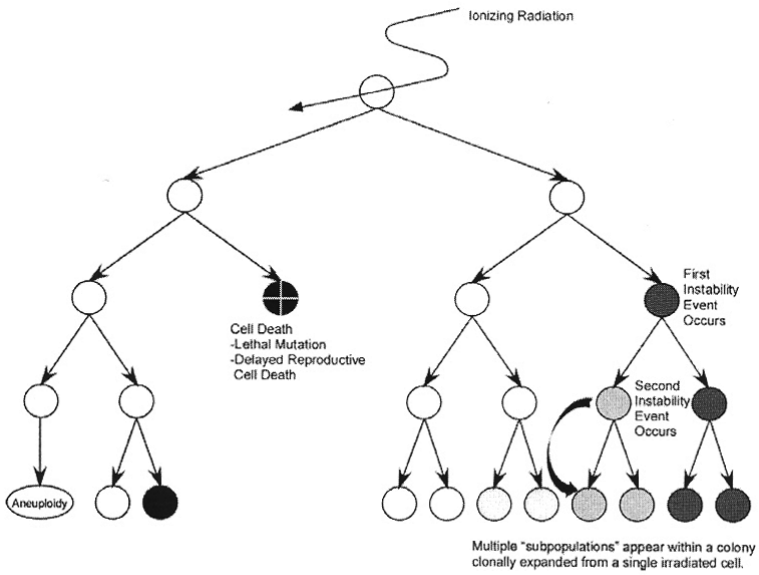
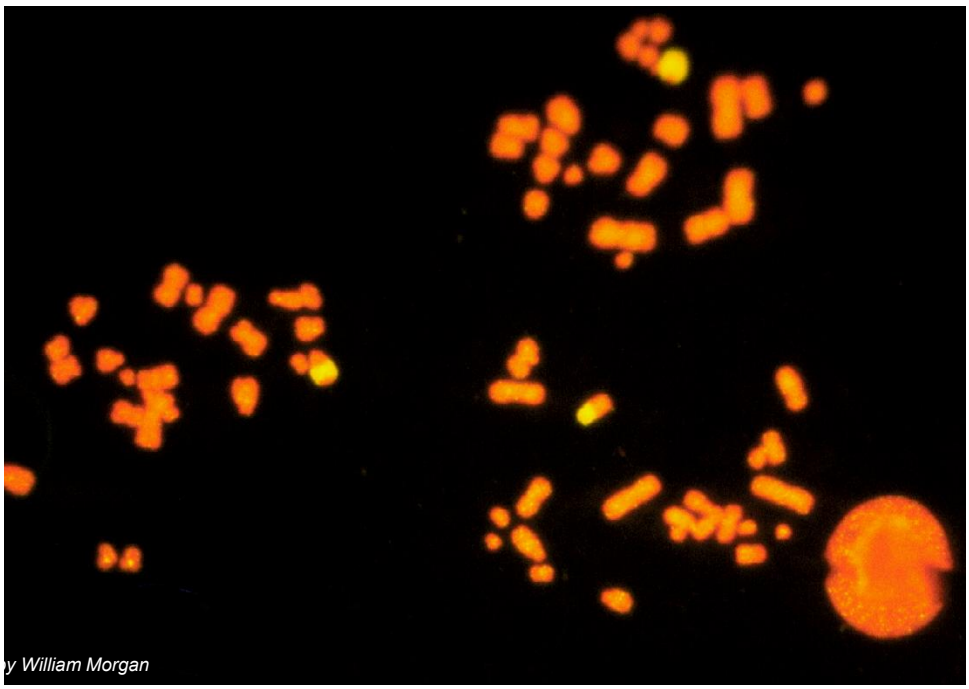


Figure II. Radiation-induced genomic instability.



II. Bystander effects and radiation exposure

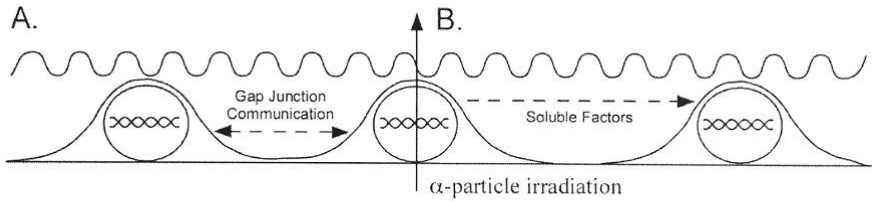
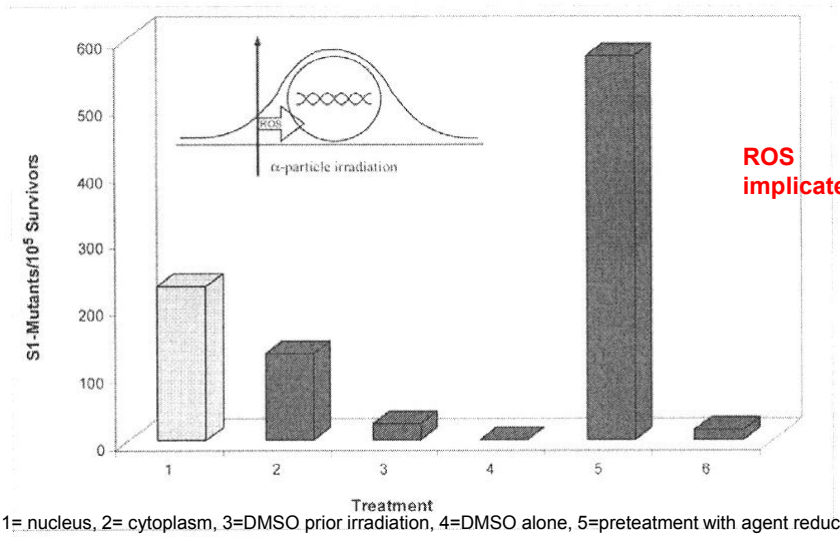


Figure V. Bystander effects are those effects occurring in cells that themselves were not directly irradiated.

Hitting the nucleus vs. the cytoplasm



1= nucleus, 2= cytoplasm, 3=DMSO prior irradiation, 4=DMSO alone, 5=preteatment with agent reducing cellular glutathione content, 6=the agent alone

Figure IV. Induced S1- mutations in human-hamster A_L cells per 10^5 survivors.

Bystander effect after irradiation with charged particle microbeam

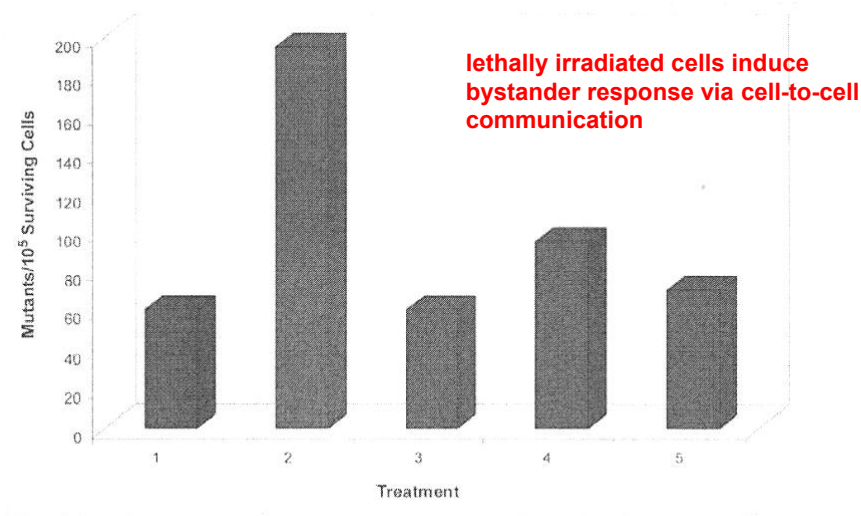


Figure VI. CD59$^-$ mutants per 10^5 surviving A_L cells.

1= unirradiated cells, 2=obs. freq. when 20% of cells exposed to lethal dose of 20 particles/cell, 3= exp.freq., 4= gap-junction inhibitor lindane + 20% cells hit, 5= lindane alone

Bystander effect after irradiation with charged particle microbeam

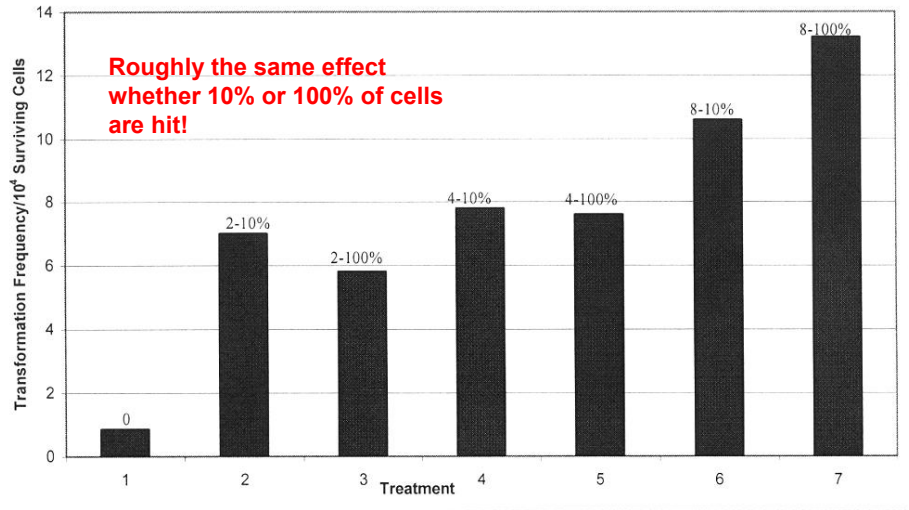


Figure VII. Transformation frequency in C3H 10T½ cells *in vitro*.

Microbeam vs. broad beam

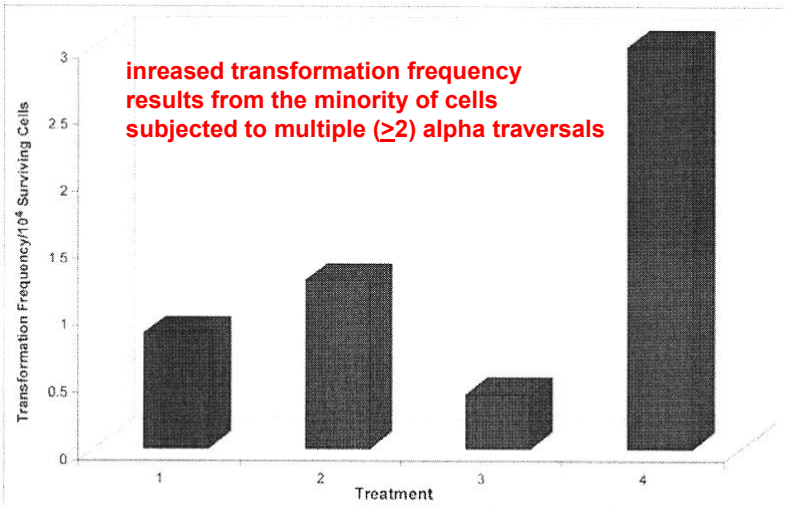


Figure VIII. Transformation frequency in C3H 10T½ cells *in vitro*.

1=control, microbeam, 2=exactly 1 alpha/cell, microbeam
3=control, broadbeam, 4=Poisson predicted 1 alpha/cell, broadbeam

Microbeam exposure: Cell killing is observed not only in hit cells

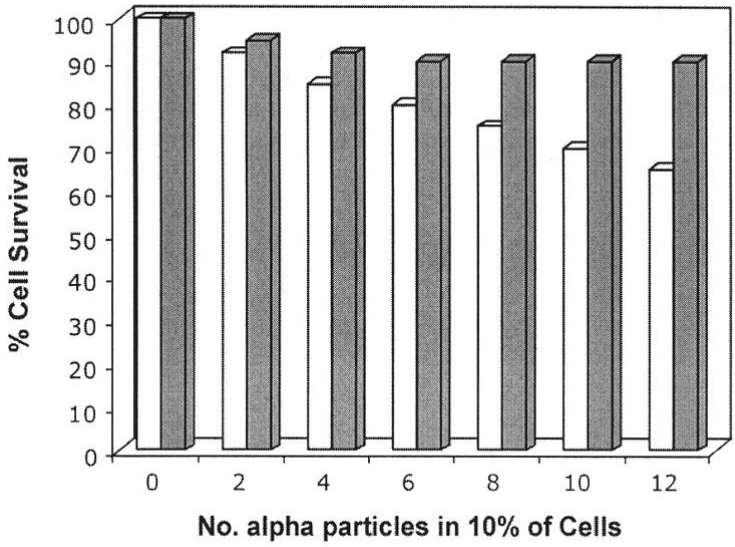
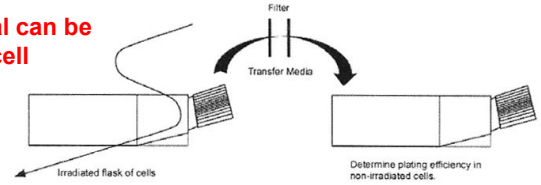


Figure IX. The bystander effect for cell survival.

open bars = experimentally determined survival
filled bars = expected survival if only irradiated cells are killed

Bystander signal can be transferred via cell culture medium



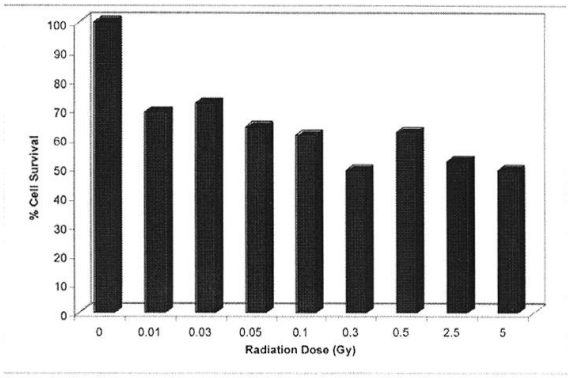
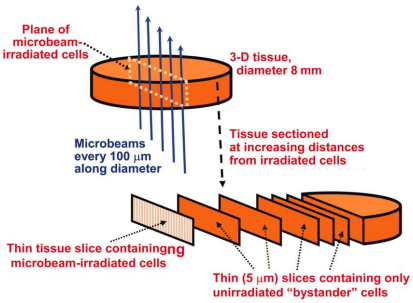
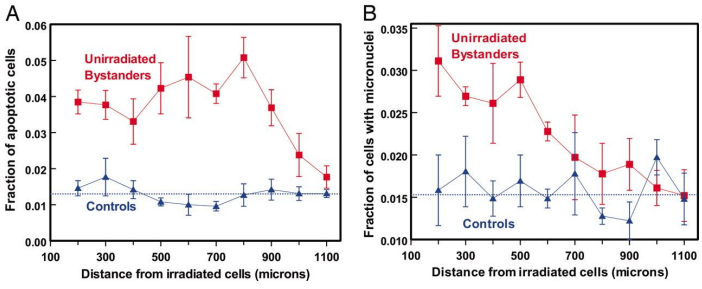


Figure X. Bystander effects in an immortalized human keratinocyte cell line as demonstrated by medium transfer experiments.

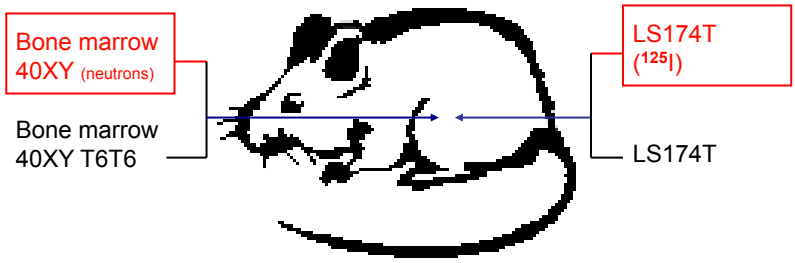
Bystander effects in an *in vivo* human skin model (3D).

Belyakov et al. PNAS 102, 14203-7 (2005)





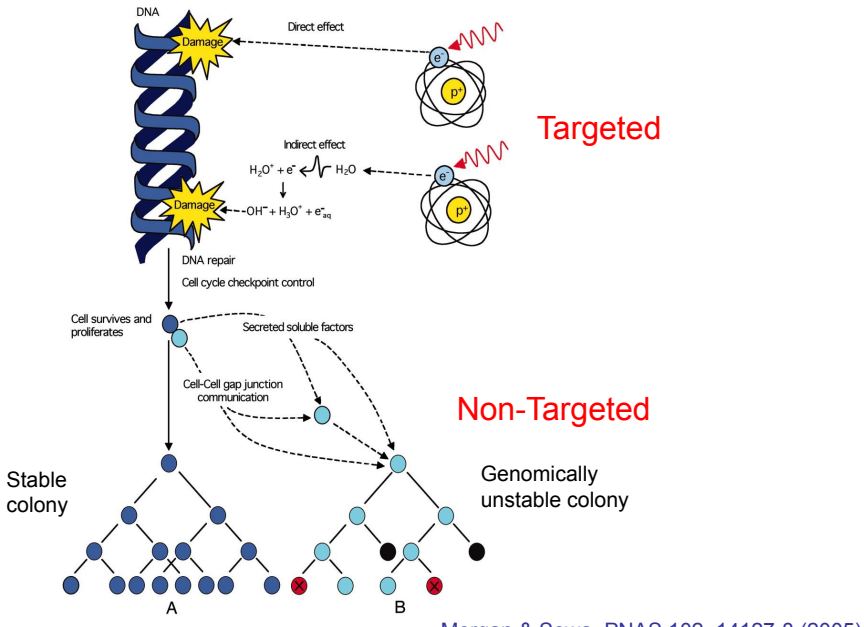
Bystander effects *in vivo*



Chromosomal instability in progeny of non-irradiated hemopoietic stem cells
Watson et al., Cancer Res. 60, 5608 - 5611 (2000)

Inhibitory effect on tumor growth
Xue et al., PNAS 99, 13765-70 (2002)

III. The relationship between radiation-induced genomic instability and bystander effects



Morgan & Sowa, PNAS 102, 14127-8 (2005)

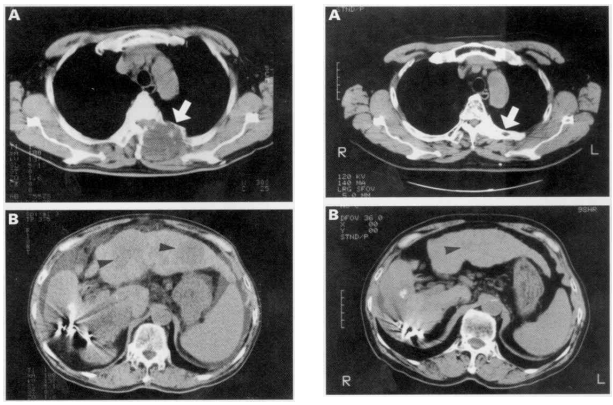
IV. Abscopal effects of radiation

Abscopal Effects:

76 year old male

Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis

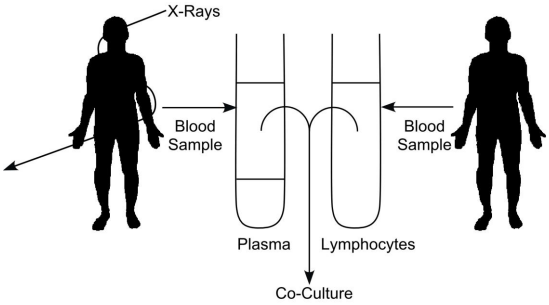
Ohba et al. Gut 43, 575-577, (1998)

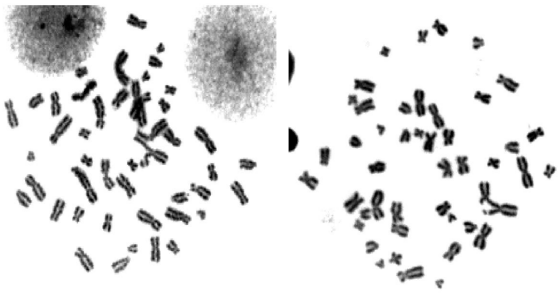


Retrospective analysis of serum concentrations of IL-1 beta, IL-2, IL-4, IL-6, HGF, and TNF-alpha

V. Clastogenic factors induced by ionising radiation

Clastogenic Factors





Clastogenic factors in plasma from:

Accidentally irradiated individuals

Goh & Sumner, Radiation Res. 35, 171-181 (1968)

Therapeutically irradiated individuals

Hollowell & Littlefield, PSEBM. 129, 240-244 (1968)

A-bomb survivors

Pant & Kamada, Hiroshima J. Med. Sci. 26, 149-154 (1977)

Chernobyl clean up workers

Emerit et al., J. Cancer Res. Clin. Oncol. 120, 558-561 (1994)

Children exposed after Chernobyl

Emerit et al., Mutation Res. 373, 47-54 (1997)

Human blood irradiated *in vitro*

Scott, Cell Tissue Kinet. 2, 295-305 (1969)

CF-Nelson rats

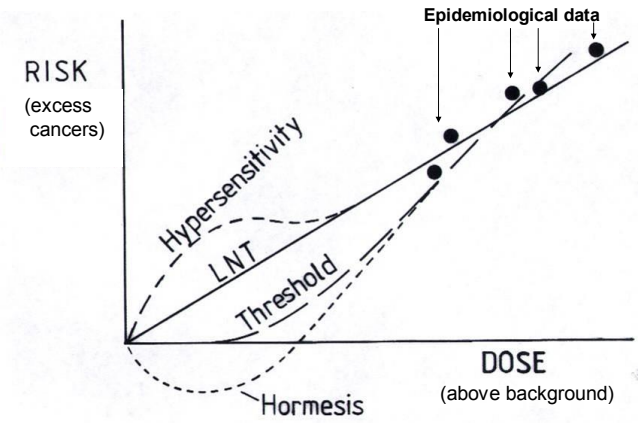
Fagnet et al., Cancer Genet. Cytogenet. 12, 73-83 (1984)

Patients with chromosome fragility syndromes

VI. The impact of non-targeted and delayed effects of radiation in the future generations

VII. Implications of non-targeted and delayed effects

Low dose risk extrapolation



Implications (UNSCEAR 2006):

- Radiation-induced instability and existence of bystander effects are well established and incontrovertible
- The relevance of non-targeted and delayed effects to carcinogenic risk and hereditary risk is not clear yet
- GI might act as a driver for progressive genetic changes associated with carcinogenesis
- BE appear limited to the irradiated organ -> risk estimates are to an organ -> BE are essentially encompassed by current risk estimates for cancer
- At low doses, risk is still uncertain and simple extrapolation from high doses may not accurately reflect the whole picture
- Past hereditary risk estimates are based on classic types of mutations; it does not appear that the new findings necessitate changes in UNSCEAR's risk estimates

Conclusions

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

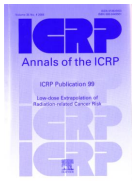
Conclusions

- The Committee continues to hold the view that mechanistic information is important for its judgements on radiation-induced health effects at doses below about 0.2 Gy.
- However, to ascribe a mechanism for the development of a particular health-related biological effect, the claw in question need to be independently replicated and to show strong coherence with the particular disease considered.
  - In this respect, the data on microdosimetric energy distribution in the cell nucleus and the subsequent cellular processing of directly induced DNA damage, reviewed in the Committee's 2000 report, are considered to provide a suitable foundation for judgements on mechanisms that affect risk estimation.
- However, the Committee recognizes that a variety of mechanistic processes will contribute to the development of radiation-induced health effects.

Future

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

ICRP Publication 99, (2005)
Conclusions, page 112



tion has not been answered scientifically and remains open.

(264) When considered as a whole, the emerging results with regard to a radiation-related adaptive response, genomic instability, and bystander effects suggest that the risk of low-level exposure to IR is uncertain, and a simple extrapolation from high-dose effects may not be wholly justified in all instances. However, a better understanding of the mechanisms for these phenomena, the extent to which they are active in vivo, and how they are inter-related is needed before they can be evaluated as factors to be included in the estimation of potential risk to the human population of exposure to low levels of IR. It should be recognised that information from direct epidemiological measure of cancer risk will, by definition, include any potential contribution from these mechanistic processes, and may therefore provide insights about them, subject to the constraints of low statistical power at low doses.

Annales de l'Association belge de Radioprotection, Vol.34, n°2, 2009
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol.34, n°2, 2009

THE BELGIAN CANCER REGISTRY, CURRENT STATE AND EPIDEMIOLOGICAL PERSPECTIVES

F.Renard
Belgian Cancer Registry

May 2009

Scope of a cancer registry

A population-based cancer registry collects systematically data about all cancer cases occurring in the population.

The first aim of a cancer registry is to monitor the frequency of new cancer cases of each type over time and space. Cancer statistics are an essential tool for cancer control policies: they aid in determining priorities, allocating resources for diagnosis and treatment, assessing the impact of preventive measures or screening programmes, and contribute to evaluate the quality of care. Abnormal variation of cancer rates detected over time or space is reported to authorities, in order to allow them to decide on additional measures or to search for causes.

Historical background and legal framework

Cancer registration began in Belgium in 1955 within the seven health insurance companies, since cancer was considered as a social disease. In 1983, a first cancer registry, the National Cancer Registry, was created as a department of the Belgian Work Against Cancer; this Cancer Registry pooled and published the data collected by the seven health insurance companies. Cancer registration at this time was not mandatory and resources were scarce, resulting in a very incomplete registration. In order to rectify this under-registration, several registration initiatives started in the Flemish region. Since 1994 to 2005, the Flemish government subsidised the development of a cancer registration network in the Flemish region, on the basis of the

integration and extension of the existing local initiatives. A collaboration with the pathology laboratories was progressively set up.
In 2005, after the dissolution of the Belgian Work against Cancer, the National Cancer Registry stopped working. The motivation of all public health authorities to get a clear insight in cancer incidence as a tool for cancer control, resulted in the creation of a new organism, the Belgian Cancer Registry Foundation, which integrated the data and the human resources from the former National Cancer Registry and the Flemish network.
Near a better financing of the cancer registration allowing to reduce the delay and under-registration in the French-speaking regions, a legal framework has been set up, making the cancer registration compulsory[1] and allowing the Cancer Registry to use the national social security number (NISS)[2]. This latter measure contributed greatly to improve the quality of the cancer registration by avoiding double counting of cases.

Methods of data collection

Since the incidence year 2004, the data flow relies on two distinct networks, the clinical network, and the pathology laboratories network, each of those notifying the cancer cases to the Registry.

The clinical network is composed of all 114 hospitals in charge of oncological pathology ("Oncological Care Programs"). Clinical registration is compulsory since the year 2003, and each case should be registered on a standard form, that can still be transmitted on paper to the Cancer Registry, but the electronic way is becoming the standard. Since the clinical registration is a time-consuming activity, it was not yet complete for the incidence years 2004-2005; the new resources allocated to the hospital registration from mid 2008 by the "Cancer Plan" of Minister Onkelinx 3 should greatly improve the clinical registration.
The pathological network is composed of all 86 pathology laboratories related to a hospital. On a yearly basis coded data from the labs, selected and extracted from the labs database, are sent electronically to the Cancer Registry.
As haematological malignancies (mostly leukaemia) are not always diagnosed in the pathological laboratory, their registration relies totally on clinical registration. For the years 2004 and 2005, the incompleteness of the clinical flow explains the under-registration of leukaemia in Wallonia.
A better exhaustiveness together with a better validity can be expected from this double flow: cases missed by one flow are expected to be declared by

the other one. Indeed, none of those flows is totally complete by itself: not all cases are microscopically confirmed (particularly in older patients, or in some difficult to reach organs such as pancreas), the extraction of the cases from the laboratory's database relies on codes that can be subject to human mistakes, and the clinical registration has started slowly. A double notification provides a confirmation of the diagnosis if the declarations are identical, and allows correcting errors in case of discrepancies.

Collected items

The following items are collected:

-Patient-related items: social security number (NISS), sex, date of birth, zipcode, encrypted code (hash code). This latter code was the historical patient identifier for the cancer registration, and resulted after encryption of sex, date of birth and last name. We keep register it beside the NISS, allowing to link relapsed cases with the initial diagnosis of the cancer in a same patient, to avoid counting them twice. Date of death is actively searched in the databases of the 'insurance companies'.

-Tumour-related items: date of incidence, the primary site, the histology, the behaviour (invasive or not), the stage and the differentiation grade. Sequence of given (or planned) treatment is also registered.

Available cancer incidence data, by year and by regions

For the historical reasons mentioned in point 2, cancer registration data in the Flemish region were available with a good level of completeness and quality much earlier than in the other parts of Belgium. We consider them as complete since incidence year 1999. For Wallonia and Brussels, data are considered as complete since 2004, with the exception of the leukaemia in Wallonia (table 1).

Main outputs

a) Incidence tables

The classical outputs of cancer registries are incidence tables[1].

The Belgian Cancer Registry produces annual incidence tables of:

- The number of new cancer cases

[1] The incidence is the number of new cases occuring in a given population within one year

- The age-specific, crude and age-standardised incidence rates[2] (European population age-standardised incidence or ESR, and World population age-standardised incidence or WSR).

All those statistics are divided by:

- Sex
- 5 years age groups
- Organ
- Country and regions. More detailed geographical levels are discussed below.

b) Maps

The Belgian Cancer Registry creates incidence maps by two different techniques:

- Administrative maps, where incidence data (standardised incidence rate) are shown by administrative level, for instance provinces, districts, municipalities. The scale of colours is divided into 19 levels, each step between categories of colour being equal to an increase of 10% in incidence.
- Semi-smoothed maps, where the incidence rate of each point is represented by its floating average. Except towns with a population over 70.000 inhabitants which are represented with their real incidence rate . The detailed methodology of those maps have been published by Pukkala and all[4, 5]; all Belgian semi-smoothed maps have been constructed by the team of the Finnish Cancer Registry. This type of maps overtakes the administrative limits of areas, and corrects for random variation typical to observations based on small populations.

[2] The crude incidence rate is the absolute number of new cancer cases occurring in a given population during one year divided by the number of people in this population. The age-specific incidence rate is the number of cancer cases in a 5 year age group divided by the number of people in this age group. Because of the variability in the age structures of different populations, a standardisation for age has to be done in order to allow for comparisons. Different standard populations can be chosen; in the Belgian Cancer registry, we calculated the standardised incidence with an European standard population (ESR), and with a world standard population (WSR).

Because of small annual events occurring when dividing territories in smaller areas, maps pool better several years together (2 to 5 years) in order to avoid too big instability of incidence rates.

Requirements to get data from the Cancer Registry

Requirements for aggregated data:

The requirements to get incidence data from the Cancer Registry by geographic levels are summarized in table 2. Regional incidence data are fully available on our website *www.registreducancer.be* .The data at provincial or district level are provided on simple request. Obtaining municipality-level data necessitates a motivated request with the description of the aims and the foreseen use of the data. Cells with fewer than 3 cases are mentioned as "<3 cases", unless the authorisation of the Committee for Privacy is obtained. The data at municipality-level can only be provided at NIS-code level (the NIS-code is the administrative code for a commune), since there is no population data at the level of ZIP-code (postcode).

To get data at a lower level (for instance statistical sector), a research protocol has to be presented to the Consultative Board of the Cancer Registry. The same conditions as for communes prevails regarding privacy. There is one additional technical step, the Registry currently doesn't have the statistical sector information nor the addresses of the patients. After obtaining the necessary authorisations, a linkage has to be done with a database of citizens addresses, for instance the health insurance companies data base.

Requirements to obtain individual data:

In some conditions specified by the law, a researcher can ask for record-level data, anonymous or coded. Requests must be addressed to the Consultative Board of the Cancer Registry and the Privacy Committee.

Examples and methodological issues

We shall illustrate the current available information from the Cancer Registry, and discuss some methodological issues and the epidemiological perspectives taking as startpoint the examples of thyroid cancer in women and leukaemia, since those cancers are generally considered as susceptible to be influenced by the exposition to ionizing radiations.

The example of thyroid cancer in women

Thyroid cancer in women represented 453 cases in 2004 and 484 in 2005 for whole Belgium. With a WSR of 6.6 for 100.000 in women, Belgium situates in the middle of the range of European rates for thyroid cancer in women.

Yet, when we look at regional incidences (table 3), we observe strong discrepancies between the regions, with 2 times higher rates in Wallonia and Brussels than in the Flemish Region.

Maps give us a better insight into the geographical distribution of the rates. Let us look at the administrative map at commune-level (figure 1): with 550 communes and less than 500 cases a year, there are many entities without cases; moreover, the random variability hides the spatial trend, if any. Rates are very instable.

If we rather look at the administrative map of thyroid cancer by district (figure 2), we see quite inhomogeneous rates within the regions; particularly high rates are observed in the districts of Neuchateau and Philippeville. Administrative maps are useful for administrative purposes, such as undertaking local public health measures, however, risk factors and cancer spread does not follow administrative limits, and are mostly inhomogeneous inside the administrative areas.

Smoothed maps can show phenomena across administrative borders; this technique allows to correct for the random variation associated to rare events, making the spatial trends visually understandable. For instance, with the semi-smoothed map of thyroid cancer (figure 3), we see a globally higher incidence in the South-east of Belgium and in Brussels, with peaks of higher incidence in the East districts and in the south-east of the Ardennes, progressively decreasing. A very high incidence is also observed in the south-west of Brussels and in Bruges.

A similar distribution of thyroid cancer rates was already described in the nineties by M.Gilbert [6] from the hospital discharges data. She examined also the distribution of surface radioactivity consequent to the Chernobyl accident (figure 4) and concluded that this geographical variation did not appear to be immediately influenced by the contamination of radioactive iodine caused by the Chernobyl accident. No geographical relationship seemed to appear with the localisation of nuclear power plants in Belgium and at the borders (figure 5).

Other hypothesis have been advanced to explain the variation of incidence in thyroid cancer between the districts, and for instance some kind of diagnosis bias: if more total glands removals are made in some parts of the country, because of more frequent thyroid pathology or because of the surgeons practices, more small unexpected thyroid cancers can be found . This hypothesis is currently explored.

Ecological versus analytical studies

This kind of reflection about the thyroid cancer rates described above is typical of what is called 'ecological studies'. In ecological studies, the unit of analysis is a population (ex: district). It is searched for a geographical correlation between aggregated rates of disease and aggregated level of exposure. Ecological studies are oversimplified models of the reality:

- The residence place is used as a surrogate for exposure, but there is no measure of the real dose.
- The residence place at the time of diagnosis is used, while the residence place at the time of exposure should be more relevant. Cancer has usually a long latency (up to 30 years) and people move. This information is hard to obtain.
- Inferences are made on individuals, assuming they have the average characteristics of the group ("Ecological fallacy")
- Confounders are not taken into account , this is a matter of concern in cancer epidemiology, where styles of life are very strong confounders and the effects of environmental risk factors are quite weak.

Anyway, ecological studies are useful to generate hypothesis or to show the need for further analysis.

In analytic studies (case-cohort and control) , the unit under study is the individual. Those studies allows in principle to adjust for confounders. On the other hand, they are more expensive and time consuming, and are more sensitive regarding privacy issues. They can be altered by observational and sequential bias .

Leukaemia in children

The aetiology of leukaemia in children rises many questions. It is still unclear if nuclear power plants or high voltage power lines can increase

leukaemia rate in children. Those questions have sometimes been asked in Belgium, but raises several methodological issues, notably:

- The underestimation of leukaemia in Wallonia for incidence years 2004-2005.
- The lack of statistical power
- The study of non administrative areas

The underestimation of leukaemia in Wallonia :

As explained above, for methodological reasons, the incidence rate of leukaemia was still underestimated in Wallonia in the years 2004-2005. Therefore it is not yet possible to show or to exclude the existence of clusters of leukaemia in the vicinity of potentially dangerous sites.

The Cancer registry is actually trying to collect the missing haematology data for the years 2004 to 2006.

The lack of statistical power

The lack of statistical power is a major concern when studying rare events, small exposure and weak excess of risk. This is typically the case in leukaemia in children and the exposition to nuclear power plants or high voltage power lines. When assuming 2% of people living within a distance of 400m of the high voltage power lines, a relative risk of 1,5, an alpha-error of 0.05 and a beta error of 0.10, the number of cases should be as high as 5000. As there are less than100 new leukemic cases in children each year in Belgium, we cannot expect to see the impact of those risk factors before decades. In England, Draper and all [7] had shown an increase in leukemic cases in children by studying 9700 cases.

Calculation of incidence in non-administrative areas

In most situations, the supposed area of exposure doesn't follow an administrative limit: for instance, the question of the increase of leukaemia in children assumes a corridor of 400 m around the high voltage power lines.

The technical issues for the computing of an incidence rate inside the corridors are:

- To get the geo-codes of the patients' residence in order to situate them within or outside the corridors.
- Geo-codes of non-cases should also be searched for in order to calculate and compare rates; this is quite uneasy since population

distribution is only available for administrative area.

Conclusions and perspectives

Incidence data are available in the Cancer Registry since 1999 (Flemish region), and 2004 (Brussels and Wallonia). Data on leukaemia are still underestimated in Wallonia. They are currently actively searched by the Cancer Registry. They should be completed by the incidence year 2007 (data reported in 2010).

Incidence data is easily available until commune-level. Incidence at statistical sector level still needs some technical work. Rates at small geographical levels are instable because they are calculated on very few observations (one additional unit may have a major impact on the rate). It is better to pool several years together. As time goes on, data on small area from the Cancer Registry will become more reliable.
Incidence across well defined administrative borders is hard to measure.

In etiological research, tables and maps helps to see the geographical patterns of spread, and can be considered as tools for generating hypothesis, but they are not sufficient by themselves to conclude in a relationship between environmental exposure and cancer.

Environmental exposure generally involve small areas, with small number of cancers. This leads to lack in statistical power. With less than 100 leukemic cases in children by year in Belgium, an eventual correlation with environmental risk factors can't be shown before decades. Maybe Belgium should participate into international studies on this topic.

Reference List

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2. Loi du 13 décembre 2006 portant disposition diverses en matière de santé. Chapitre VI, article 39. Moniteur Belge 2006;73786-73789.
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4. Pukkala E GNTL. Atlas of cancer incidence in Finland 1953-82. Cancer Society of Finland publication ed. Helsinki: 1987.
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6. Gilbert M, Thimus D, Malaise J et al. Is there an increased incidence of surgically removed thyroid carcinoma in Belgium 10 years after Chernobyl? a study of hospital discharge data. Acta chirurgica Belgica 2008; 108:318-322.
7. Draper G, Vincent T, Kroll ME, Swanson J. Childhood cancer in relation to distance from high voltage power lines in England and Wales: a case-control study. BMJ 2005; 330(7503):1290.

Table 1 : Available incidence data by year and region

	Flemish Region	Walloon Region	Brussels Region
1999	Yes		
2000	Yes		
2001	Yes		
2002	Yes		
2003	Yes		
2004	Yes	Yes (but leukemia)	Yes
2005	Yes	Yes (but leukemia)	Yes

Table 2 : Availability of data and requirements by geographical level

	Availability	**Procedure**
Country, regio	Published (website, brochure)	-
Provincie	Yes	Simple request
District	Yes	Simple request
Municipality (NIS code)	Yes	Motivated written request. Evaluation of the request. Signed agreement for the use of the data In case of small number, authorisation from the privacy committee
Statistical sector	More technical work needed	Idem + authorization to link with a data bank of statistical sectors

Table 3: **thyroid cancer in women by region, incidence year 2004-2005**

	Absolute numbers	**Crude rate (for 100.000)**	**European standardised rate**	**World standardised rate**	**SIR**
Flanders	**399**	**6.53**	**5.83**	**4.84**	**Token as reference**
Wallonia	**403**	**11.55**	**10.87**	**8.85**	**180.89**
Brussels	**135**	**12.95**	**12.89**	**10.44**	**206.25**

Figure 1 : age-standardised incidence of thyroid cancer in women by commune, administrative map 2004-2005

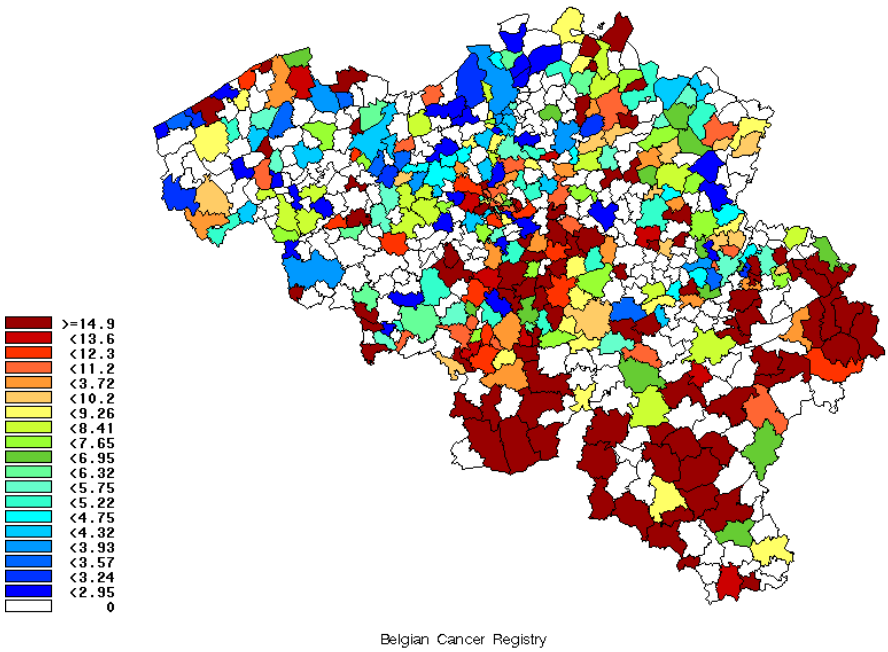

Figure 2: age-standardised incidence of thyroid cancer in women by district, administrative map 2004-2005

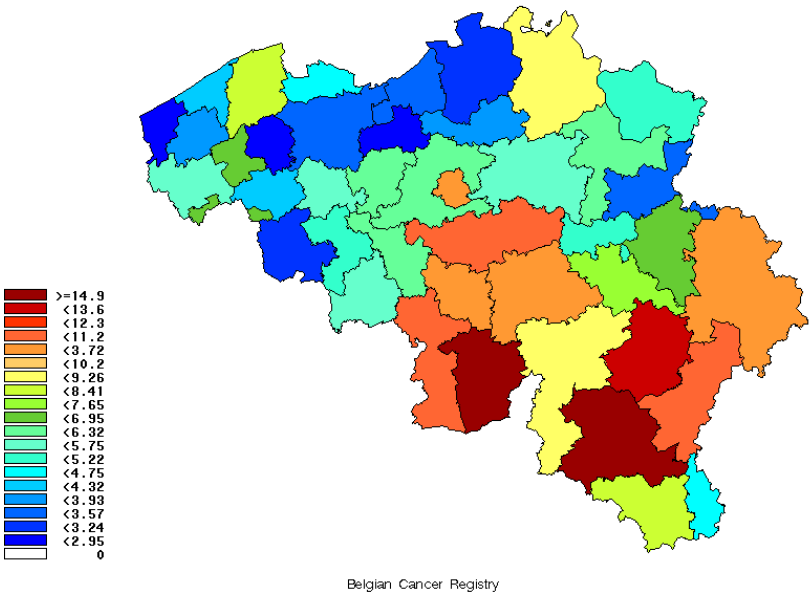

Figure 3 : thyroid cancer in women, semi-smoothed map 2004-2005

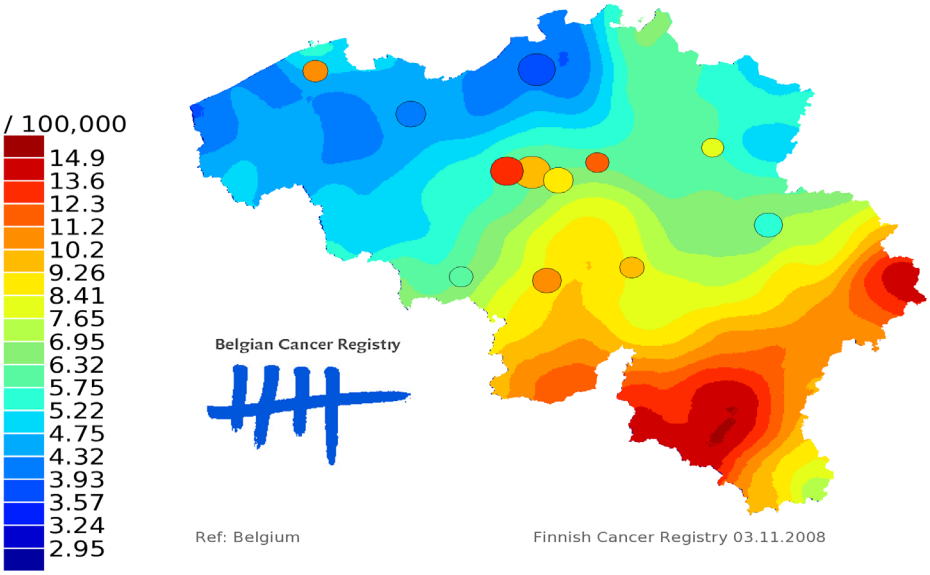

Figure 4 : distribution of surface radioactivity after Tchernobyl, Belgium (SCK-CEN)

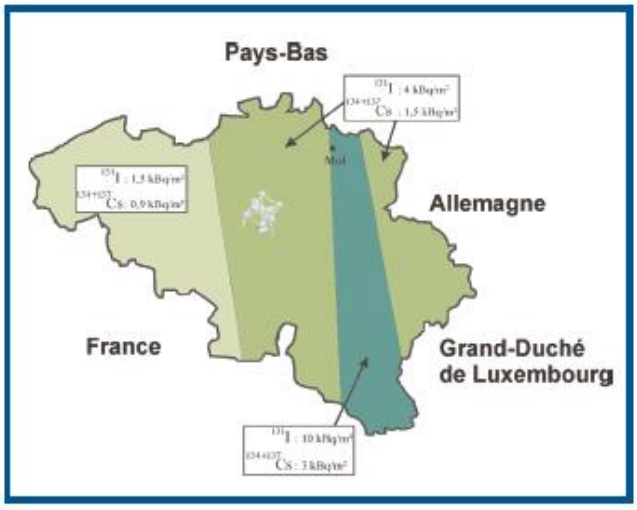

Figure 5 : main nuclear sites, Belgium and border of neighbouring countries