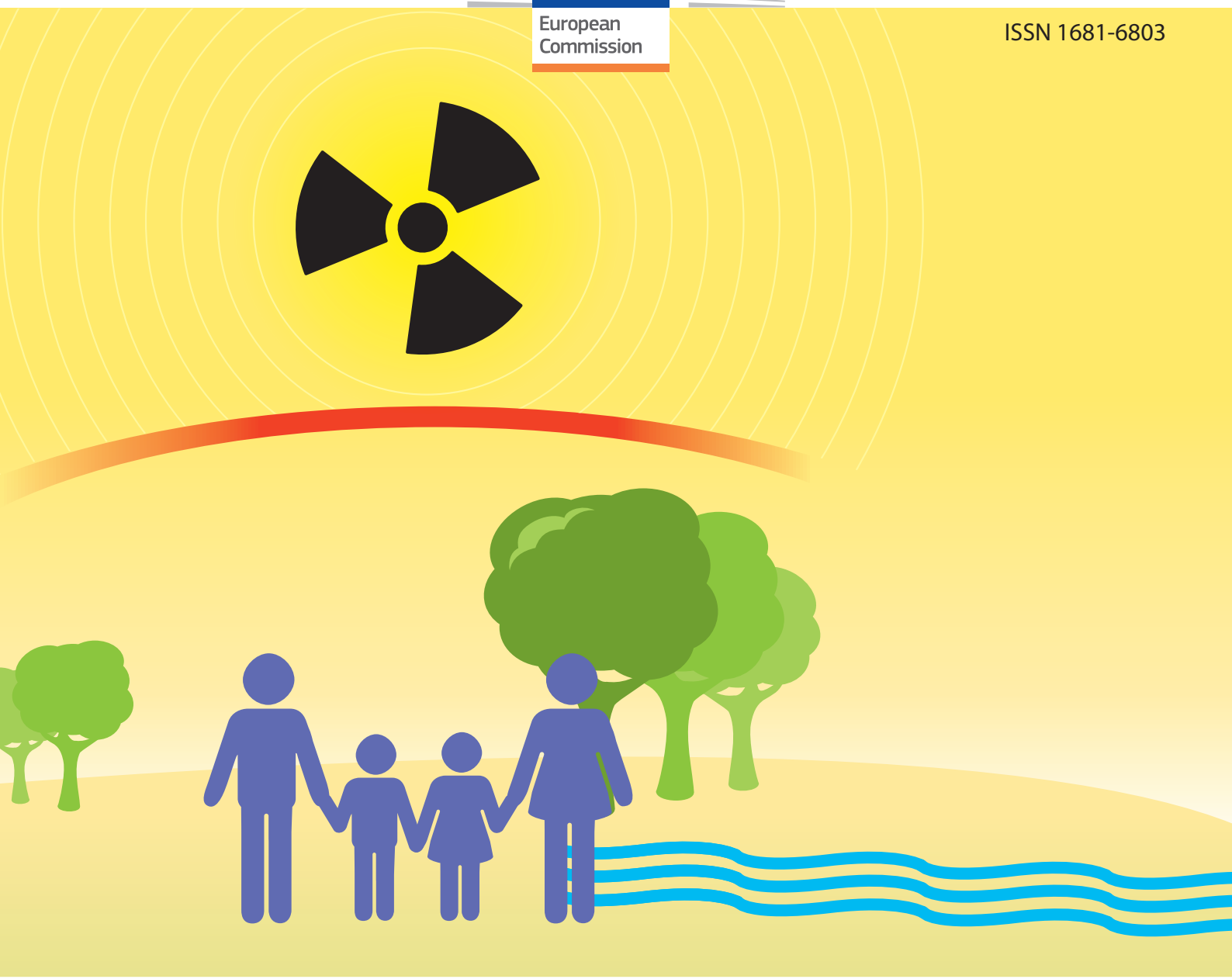
European Commission

ISSN 1681-6803



# Radiation Protection

*No 168*

*EU Scientific Seminar 2010*
*'Issues with internal emitters'*

*Energy*

EUROPEAN COMMISSION

# RADIATION PROTECTION N° 168

## EU Scientific Seminar 2010

## "Issues with internal emitters"

Proceedings of a scientific seminar held in Luxembourg on 23 November 2010

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

Directorate-General for Energy
Directorate D — Nuclear Safety and Fuel Cycle
Unit D3 — Radiation Protection
2013

***Europe Direct is a service to help you find answers to your questions about the European Union***

**Freephone number (*):**
**00 800 6 7 8 9 10 11**

(*) Certain mobile telephone operators do not allow access to 00 800 numbers or these calls may be billed.

More information on the European Union is available on the Internet (http://europa.eu).

Luxembourg: Publications Office of the European Union, 2013

ISBN 978-92-79-28682-7
doi: 10.2768/22829



*Printed in Luxembourg*

# FOREWORD

Luxembourg, October 2012

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

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

In 2010, the Scientific Seminar discussed *Issues with Internal Emitters*. Five internationally renowned scientists working in the field of internal emitters presented current knowledge. The speakers offered information on dosimetry, uncertainties, and risk estimates in the context of internal emitters, on progress in understanding radon risk, on the less known Thorium-232 decay chain, and on an update on lessons learnt from thyroid cancers after the Chernobyl accident. The presentations were followed by a round table discussion, in which the speakers and invited additional experts discussed potential *policy implications and research needs*.

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

Augustin Janssens
Head of Radiation Protection Unit

# CONTENTS

# 1 THE ISSUE OF DOSIMETRY AND UNCERTAINTIES IN THE CONTEXT OF INTERNAL EMITTERS

**Eric Blanchardon**

***IRSN - Institute for Radiological Protection and Nuclear Safety, France***

*Abstract*

*Internal dosimetry is based on the measurement of activity in the environment and individuals. Biokinetic and dosimetric models represent the behaviour of radionuclides in the body and the consequent deposition of energy in the radiosensitive target tissues. Measurement results are interpreted into committed effective dose through application of the models. However, significant uncertainties are involved at each step of the process due to counting statistics, variable measurement efficiency, environmental and biological fluctuations, incomplete biokinetic, physical and anatomic datasets, simplified models, heterogeneous distribution of radionuclides, energy deposition and target cells in tissues. These uncertainties can lead to discrepancies in dose assessments but may be quantified by mathematical methods such as Bayesian inference. Further research is warranted to reduce those uncertainties and to harmonize their management.*

## 1.1 Introduction

The dosimetric quantities are not directly measurable in the human body. For external irradiation they are derived from operational dose quantities through conversion factors. In case of internal exposure, the process is even more indirect as only activities are measured and then converted into dose through biokinetic models. In prospective dosimetry, the intake of radionuclide is derived from the level of environmental contamination while in retrospective dosimetry it is inferred by the measurement of activity retained in the body or excreted in urine or feces.

Ionizing radiation interacts with matter by imparting energy. The quantity of imparted energy by unit of mass is the absorbed dose. Its SI unit is $J.kg^{-1}$ and its special name is gray (Gy). It is an average of energy imparted by point interactions over a defined volume and time. For radiation protection purpose, the absorbed dose is averaged over an organ (liver), a tissue (muscle) or the sensitive target cells within a tissue when those are identified: stem cells of the alimentary tract (ICRP, 2006), basal and secretory cells of the bronchi (ICRP, 1994a), red bone marrow and endosteal surfaces of skeleton (ICRP, 1995b).

The equivalent dose in a region $T$, $H_T$, is defined as:

$$H_T = \sum_R w_R D_{T,R}$$

where $D_{T,R}$ is the average absorbed dose in region $T$, due to radiation of type $R$. $w_R$ is the radiation weighting factor for radiation $R$. The unit of equivalent dose is the sievert (Sv). $w_R$ values result from a judgment based on the knowledge of the relative biological effectiveness of the different radiations. $w_R$ is equal to 1 for photons and β, to 20 for α particles and takes situation-specific values for Auger electrons (ICRP, 2007).

The effective dose $E$ is defined as a weighted average of equivalent doses to radiosensitive tissues of the body:

$$E = \sum_t w_T H_T = \sum_T \sum_R w_R D_{T,R} \ ,$$

where $w_T$ is the tissue weighting factor for $T$, with the sum of $w_T$ being 1. The values of $w_T$ are set by judgment on the basis of epidemiological data of Hiroshima-Nagasaki survivors considering the frequency of stochastic effects and their severity in the different tissues (ICRP, 2007).

Radionuclides incorporated in the body may irradiate the tissues for a long time after incorporation depending on their physical half-life and their biological retention. So the committed effective dose $E_T(\tau)$ is defined as the total dose delivered over the time period $\tau$ following intake of a radionuclide. $\tau$ is usually set to 50 years for adults and up to the age of 70 for children so as to cover life-long irradiation (ICRP, 2007).

## 1.2 Activity measurement

### 1.2.1 Environmental contamination

The main route of public exposure is the ingestion of radionuclides in contaminated diet or water. This is therefore controlled by activity measurement of environmental matrices, including food stuff and drinking water, both in normal situation and in case of nuclear incident or accident (Champion and Peres, 2009).

Under a regulation of the European Union (EU), based on the European Atomic Energy Community Treaty of 1957, Member States are obliged to monitor radioactivity levels in the environment of their countries and to regularly report the measured values to the European Commission (EC). Networks for routine and emergency measurement of radioactivity values have been established, and details of what environmental matrices and food samples are to be monitored for which radionuclides are specified in several Commission Recommendations. In order to verify the quality of the values reported by the Member States and their comparability amongst each other, measurement comparison exercises have been conducted since 1991 by the EC through its Joint Research Centre. EU laboratories involved in monitoring radioactivity in the environment and food stuffs are urged to participate in such comparisons relevant to their routine measurement tasks in order to demonstrate their measurement capabilities (Wätjen et al. 2007; Wätjen et al. 2008a; Wätjen et al. 2008b).

Inhalation of radioactive aerosols is the main route of occupational exposure. As a consequence, static air samplers (SAS) are commonly used to monitor workplace conditions, but can underestimate concentrations in air in the breathing zone of a worker. Apart from their potential use for dose estimation, SAS devices can also provide useful information on radionuclide composition, and on particle size if used with a size analyser such as a cascade impactor.

A more precise estimate of the contamination of the air actually breathed by a worker can be obtained from a personal air sampler (PAS). Such portable device includes a sampling head containing a filter worn on the upper torso close to the breathing zone. Air is drawn through the filter by a calibrated air pump carried by the worker. The filter may be measured at the end of the sampling period to give an indication of any abnormally high exposures. The filters can then be retained, bulked over a longer period, and the activity determined by radiochemical separation and high sensitivity measurement techniques.

In prospective dosimetry, the exposure may also be forecast by measurement of surface activity with an adapted nuclear probe or through a smear test and application of a resuspension factor (Boulaud et al. 2003).

### 1.2.2 Individual measurement

In order to quantify individual contamination, two approaches can be applied: *in vivo* or *in vitro* measurements. *In vivo* measurement is the direct measurement of body content of radionuclides by detectors set outside the body (Fig. 1). It provides a quick (20-30 minutes) estimate of activity in the body or in a specific organ. But it is feasible only for radionuclides emitting radiation that can escape from the body. In principle, the technique can be used for radionuclides that emit X, γ or energetic β particles.

**Figure 1** ***In vivo*** **measurement and efficiency calibration using a physical (bottle) phantom in the mobile in vivo counting laboratory of IRSN**

*In vitro* or indirect measurement is the analysis of excreta or another biological sample (nose blow, nasal smear, blood or biopsy). It is the only measurement approach for radionuclides which emit no penetrating radiation (e.g. high energy photons). Urine and faeces measurements are widely used because of their high sensitivity and applicability to any radionuclide. However, α spectroscopy usually requires a one-week-long chemical process and sample counting for several days. Furthermore, *in vitro* measurement may be performed without the worker leaving the workplace but involves a risk of sample contamination.

For both techniques, activity measurement is done by the interactions of emitted radiations within a detector. These interactions are converted into electric impulses (counts) by the detector. The number of counts ($N$) can be converted in activity ($A$ in Bq) through the efficiency of detection of the detector ($\varepsilon$), the emission yield of the radiation ($Y$) and the counting time ($T_{count}$ in seconds):

$$A = \frac{N}{T_{count} \times Y \times \varepsilon}$$

For *in vitro* measurements, the chemical yield of the preparation $Y_c$ must be added:

$$A = \frac{N}{T_{count} \times Y \times Y_c \times \varepsilon}$$

The efficiency of detection, or calibration coefficient, is evaluated by measuring a source of known activity with the same geometry as the actual measurement. For *in vivo* measurements, phantoms are used to simulate the human body (Fig. 1). The performance

criteria of these measurements can be assessed by applying the ISO standard 12790-1 (2001).

### 1.2.3 Monitoring programme

For occupational exposure the International Organization of Standardization (ISO, 2006) recommends workplace monitoring if the likely annual committed effective dose exceeds 1 mSv and individual monitoring if it exceeds 6 mSv. The standard defines requirements to be followed in the design of a routine monitoring programme:

- The consequence resulting from an unknown time interval between intake and measurement shall be limited so that, on average over many monitoring intervals, doses are not underestimated and the maximum underestimate of the dose resulting from a single intake does not exceed a factor of three.
- The detection of all annual exposures that can exceed 1 mSv shall be ensured.
- At least two measurements shall be performed annually.

These criteria are in agreement with the recommendations of the IAEA (1999) and of the ICRP (1997). They are applied to select measurement techniques and monitoring intervals. Consistently, suitable monitoring programmes are proposed for different radionuclides.

## 1.3 Models

### 1.3.1 Biokinetic models

To interpret activity measurements, the behaviour of radionuclides from intake to elimination are described by biokinetic models. These are made of compartments corresponding to organs, tissues, metabolic states or fractions of activity within a tissue, and transfers of activity between compartments governed by first order kinetics with constant rates estimated from animal experiments or follow-up of human contamination cases. The biokinetic models translate into a set of linear first order differential equations. They allow predicting from a given intake, the retention of activity in organs and its excretion in urine and faeces as functions of time. The integral of retained activity over the commitment period provides the number of nuclear transformations that take place in a region. Specific models have been developed by the ICRP to describe radionuclides behaviour at the site of entry, with kinetics of transfer into the blood following inhalation, ingestion or wound, and the element-specific systemic kinetics of exchange between blood and tissues and the excretion.

#### *1.3.1.1 Human Respiratory Tract Model*

The Human Respiratory Tract Model (HRTM) (ICRP, 1994a) describes the morphology and the physiology of the respiratory tract, the deposition of an inhaled radionuclide in the different regions of the airways, and the clearance of the deposited activity.

The morphology of the respiratory tract defines the different compartments used in the model (extra-thoracic, ET; bronchial BB; bronchiolar, bb; and alveolar-interstitial, AI). Deposition is the process that determine how much of the intake remain in the regions of the respiratory tract after inhalation and exhalation of an aerosol. The HRTM deposition model represents airways as a succession of filters where a fraction of particles is deposited during inhalation and exhalation. Deposition can occur as a consequence of gravitational sedimentation, inertial impaction and Brownian motion (diffusion). Sedimentation and impaction are aerodynamic effects that are important for particles with diameters above about 0.1 µm and

increase with size. Diffusion is a thermodynamic effect that is important below about 1 µm and increases with decreasing size.

In practice, aerosols are almost never composed of particles with a single size (monodisperse) but include rather of a mixture of particle sizes (polydisperse). The mass of particles in aerosols is usually log-normally size-distributed (ICRP, 2002a). The log-normal distribution is described by two parameters: the median diameter and the geometric standard deviation. For radioactive aerosols, it is convenient to refer to the activity median diameter of the aerosol. For particles larger than 0.1 µm, the Activity Median Aerodynamic Diameter (AMAD) is used to define an aerosol size distribution: 50% of the activity in the aerosol is associated with particles of aerodynamic diameters larger than the AMAD. Activity Median Thermodynamic Diameter (AMTD) is used to characterize particle distributions below 1 µm. AMAD and AMTD are the main parameters influencing the amount and the repartition of deposited particles in the respiratory tract. Physiological parameters such as the breathing rate, which depends on the level of exercise, the regional airways volumes and the fraction of air breathed through the nose also influence deposition and can be set to reference values suggested by the ICPR (1994a).

Clearance is due to the mucociliary transport of the deposited particles up to the alimentary tract in competition with transport to the regional lymph nodes and with absorption into blood. Mechanical particle transport rates are determined by ongoing biological processes, such as the flow of fluids over airway surfaces, which are generally unaffected by the deposited material. Particle transport rates are therefore assumed to be the same for all materials.

Absorption is assumed to take place at the same rate throughout the respiration tract and depends on the physical and chemical form of the deposited material. It is a two-stage process: dissociation of material that can be absorbed into blood (dissolution); and uptake into blood. Dissolution may be modelled by three parameters: a fraction $f_r$ of the activity is rapidly dissolved at a rate $s_r$, the remaining fraction $(1 – f_r)$ is dissolved at a slower rate $s_s$.

The ICRP recommends default values of these parameters for reference absorption types: Type F (fast), corresponds to rapid absorption of the radionuclide with a half-time of about 10 min ($f_r$ = 1, $s_r$ = 100 $d^{-1}$); for Type M (moderate), 10 % of the activity is absorbed with a half-time of 10 min and 90 % with a half-time of 140 d ($f_r$ = 0.1, $s_r$ = 100 $d^{-1}$ and $s_s$ = 0.005 $d^{-1}$); for Type S (slow), 0.1 % is absorbed with a half-time of 10 min and 99.9 % with a half-time of 7000 d ($f_r$ = 0.001, $s_r$ = 100 $d^{-1}$, $s_s$ = 0.0001 $d^{-1}$) (ICRP, 1994a). In the absence of more specific information, one of the reference types can be chosen according to the chemical form of the radionuclide. Uptake of dissolved material into blood is usually treated as instantaneous.

#### *1.3.1.2 Human Alimentary Tract Model*

Material may reach the alimentary tract (HAT) either directly by ingestion or indirectly by transfer from the respiratory tract or from systemic circulation, mostly through the liver. The Human Alimentary Tract Model (HATM) of the ICRP (2006) consists of seven sections (oral cavity, oesophagus, stomach, small intestine, right colon, left colon, rectosigmoid colon) to predict faecal excretion, absorption into blood and number of nuclear transformations of radionuclides. The transfer rates between sections depend on age, diet and sex. The small intestine is assumed to be the main site of absorption to blood while some local retention and absorption to blood may occur in the mouth, stomach, colon and small intestine. The absorption is quantified by the fraction $f_A$ of activity reaching blood following entry in the HAT.

#### *1.3.1.3 Wound Model*

A biokinetic model for radionuclide-contaminated wounds was developed by the US National Council on Radiological Protection and Measurements (NCRP) (2006). The NCRP wound model consists of seven compartments describing metabolic states of activity retained within the wound site and clearance to blood and lymph-nodes.

Repartition between the compartments, retention at the wound site and transfer to the lymph nodes depends on the physical (solution, colloid, particles, fragment) and chemical form of the compounds. Four default categories for soluble compounds are defined: weak, moderate, strong and avid in which radionuclides may be grouped roughly according to their tendencies for hydrolysis or forming stable complexes with biological ligands at neutral pH. Insoluble compounds are retained much longer at the wound site, with significant transfer of particles to the lymph nodes and tissue reaction around fragments. The model allows the estimation of retention of radionuclide at the wound site and its uptake into blood as a function of time.

#### *1.3.1.4 Systemic models*

A systemic model describes the behaviour of radionuclide since its uptake in blood. Systemic circulation distributes the radionuclide in different body tissues where it can be retained for a period depending on the element. As an example, the main target organs of plutonium are skeleton and liver (ICRP, 1993). Plutonium is strongly retained in the skeleton and very slowly excreted.

From recent plutonium injection studies and follow-up of Mayak plutonium workers, Leggett and co-workers developed an improved systemic model (Leggett *et al*, 2005). The proposed model contains separate blood compartments for uptake and recycling of activity and a third liver compartment, resulting in increased early and intermediate retention in liver.

### 1.3.2 Dosimetric models

#### *1.3.2.1 Formalism*

In order to assess effective dose, absorbed doses in tissues are calculated by dosimetric models. According to Bolch et al. 2009, the cumulated activity $\tilde{A}(r_S,T_D)$ in a source region $r_S$ is the number of nuclear transitions over the commitment period $T_D$:

$$\tilde{A}(r_S,T_D)=\int_0^{T_D} A(r_S,t)\cdot dt$$

where $A(r_S,t)$ is the activity of the radionuclide in $r_S$ at time $t$.

At each nuclear transition, $Y_i$ radiations $i$ or energy $E_i$ are emitted. A fraction $\Phi(r_T \leftarrow r_S,E_i)$ of this energy is absorbed in each target region $r_T$ of mass $M(r_T)$.

A radionuclide-specific factor $S(r_T \leftarrow r_S)$ can then be defined as

$$S(r_T \leftarrow r_S)=\frac{1}{M(r_T)}\sum_i E_i Y_i \phi(r_T \leftarrow r_S,E_i)$$

And the dose $D(r_T,T_D)$ absorbed by $r_T$ during $T_D$ can be expressed as

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D) S(r_T \leftarrow r_S)$$

The calculation of absorbed dose therefore requires the definition of a source region $r_S$, a target region $r_T$, the estimation of the cumulated activity $\tilde{A}$ in the source region, the calculation of the energy spectrum $\{E_i, Y_i\}$ and its transport from the source region to the absorbed region via the absorbed fraction $\Phi$. The cumulated activity is obtained from the biokinetic models. The energy spectrum is recorded in dedicated databases (ICRP 2008). For radiation protection purpose, the source and target regions are defined according to a reference person whose parameters are median values of the general population (ICRP 2002b).

#### *1.3.2.2 Principle*

The absorbed fractions are calculated by applying Monte-Carlo codes of radiation transport to anthropomorphic computational phantoms representing the reference person. The current dose coefficients of the ICRP (ICRP 1998) are based on stylized phantoms described by mathematical equations (Cristy and Eckerman, 1987). These are now replaced by voxel phantoms based on medical images of real persons (ICRP, 2009).

The Monte Carlo method consists in the generation of a large number of stochastic histories according to density probabilities describing the actual phenomena of radiation-matter interaction and in the estimation of the quantities of interest from discrete sums approximating the corresponding integrals. The Monte Carlo codes of radiation transport use the experimental nuclear and atomic data of differential cross sections to sample the probability density functions of the random variables characterizing the history, or track, of a particle: its mean free path between interaction events, the types of interaction, the energy loss and deviation angle of the particle from a given event, the initial state of the possible secondary particles. The simulation of the transport is performed with approximations related to the slowing and diffusion processes. Calculation codes differ in the input data they use and in the approximations on the physics. The principal codes applied to internal dosimetry are MCNP (Briesmeister, 2000), MCNPX (Hendricks *et al.*, 2008), EGS4 (Nelson *et al.*, 1985), EGSnrc (Kawrakow and Rogers, 2001), PENELOPE (Salvat *et al.*, 2006) and GEANT4 (Geant4 Collaboration, 2003). They are limited by computation times from several hours to several days to obtain a proper statistical convergence and by the availability of basic physical data.

#### *1.3.2.3 Local geometry*

In most organs and tissues, the local activity as well as the radiosensitive target cells are assumed to be uniformly distributed. However, in a few specific tissues, the identification of the radiosensitive cells allow for a more precise definition of the source and target geometry of irradiation, which is mainly of concern for short range alpha and beta particles.

The target cells identified in the thoracic region include basal and secretory cells in the bronchial epithelium; clara cells (a type of secretory cell) in the bronchiolar epithelium; and endothelial cells such as those of capillary walls and type II epithelial cells in the AI region. The dose to each region is given by the average dose to the target tissue in that region. For the BB region that contains both basal and secretory cells, which lie at different depths, HRTM assumes that both cell populations have equal sensitivity to dose. Thus the absorbed dose to the BB region is given by:

$$D_{BB} = 0.5\ D_{bas} + 0.5\ D_{sec}$$

For the AI region it is assumed that the target cells are distributed homogeneously throughout the tissue mass so the average dose to the target cell in the AI region can be assumed as that received by the whole tissue mass.

To take account of differences in sensitivity between tissues, each regional dose is multiplied by an apportionment factor, $A_i$, representing the region's sensitivity relative to that of the whole organ. The absorbed dose to the lung (thoracic airways) arising from the inhalation of radionuclide is given by:

$$D_{lung} = D_{BB}A_{BB} + D_{bb}A_{bb} + D_{AI}A_{AI}$$

Because of the lack of data and the difficulty in determining the sites of origin of the major lung cancer type, ICRP assumed $A_i$ for each of the three regions to be equal to 0.333. In other words each of the three regions is assumed to be equally sensitive to dose. This does, however imply far higher sensitivities per unit mass for BB and bb than for AI, because of their much lower masses.

The human alimentary tract model (ICRP, 2006) also includes dosimetric models for the walls of the tract. In these models, the target tissues are not considered to be the whole wall but radiosensitive tissues in the epithelium of the stomach wall lying in a depth between 60 and 100 mm from the content of the stomach and stem cells in the bases of the crypts of the colon, 280–300 mm deep from the content of the colon compartments. In this geometry, alpha emissions in the contents of the alimentary tract in general will not deposit energy within the target tissues of the wall. The colon dose used for the calculation of the effective dose is the mass-weighted average dose to the three colon segments.

The radiosensitive cells of the skeleton are the haematopoietic stem cells of the red bone marrow for the induction of leukaemia and the endosteal cells within a 50 µm layer adjacent to the surfaces of the medullary cavities of the long bone and of the trabecular bone for bone cancer induction. Within the spongious region of the bones, inactive yellow marrow, active red marrow, endosteum and mineral trabecular bone are imbricated at microscopic scale, inducing electron disequilibrium and complex dosimetry (Fig. 2). An update of skeletal dosimetry accounting for the macrostructure and microstructure of the different bones including the relative proportion of red and yellow marrow is being developed at the University of Florida (Pafundi et al. 2010).

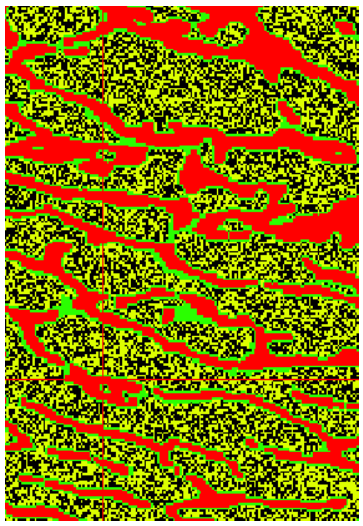


**Figure 2 Micro-computed tomography image of a human right scapulae slice after voxelisation with OEDIPE software (Chiavassa et al. 2005) and adjustment of yellow marrow to red marrow ratio at 50% cellularity. Red: trabecular bone, black: active bone marrow, yellow: inactive marrow, green: endosteum. 50 µm voxels.(Lama Hadid, personal communication)**

## 1.4 Dose calculation

### 1.4.1 Principle

To assist in the calculation of effective dose from activity measurement, the ICRP has published excretion and retention functions as the prediction of the biokinetic models for the measured parameters (body content, organ content or daily excretion) after a unit intake and dose coefficients as the committed effective dose received by the reference person from a unit intake. To choose the retention and excretion functions as well as the dose coefficient adapted to the situation, it is necessary to know or to assume conditions of exposure: radionuclide(s), isotopic composition, intake time, intake route (inhalation, ingestion, wound), physico-chemical properties of the radioactive material (absorption type, AMAD for an aerosol).

From a known environmental contamination, the intake of radionuclide can be determined according to the habits of the exposed individuals. For instance, the incorporation *i* of radionuclide from a time *T* spent in a atmosphere contaminated at a concentration *C* may be derived through the breathing rate *B* as:

$$i = C \times T \times B$$

From an individual measurement *M* of activity retained or excreted *t* days after incorporation, the intake *i* is estimated by dividing *M* by the value *m(t)* of the retention or excretion function derived from the biokinetic model for unit intake*:*

$$i = \frac{M}{m(t)}$$

If multiple measurements are available, a best estimate of intake may be obtained by applying a statistical fitting method.

The committed effective dose *E* is calculated by multiplying the intake by the dose coefficient $e_{50}$:

$$E = i \times e_{50}$$

### 1.4.2 Reference values

Exact values for all or some of the parameters of dose calculation are generally unknown and often difficult to investigate. The ICRP therefore recommends the use of representative default values. In the absence of specific information, the individual is represented by the reference person of the ICRP (ICRP 2002b); a worker has an occupational activity 8 hours a day, with a breathing rate of 1.2 $m^3.h^{-1}$ (ICRP, 1994a); the pulmonary absorption of the material is either type F, M, or S (ICRP, 1998); the absorption from the gut is quantified by a proposed value of $f_A$ (ICRP 2006); the AMAD of a radioactive aerosol is 5 µm for workers with a geometric standard deviation of 2.5 and a density of 3 $g.cm^{-3}$ (ICRP, 1994a); in routine monitoring, the contamination is assumed to have occurred at the middle of the monitoring interval (ICRP, 1997).

## 1.5 Uncertainties

The assessment of effective dose due to a contamination from bioassay data is subject to uncertainty up to several orders of magnitude (CERRIE, 2004). Even though there is no quantitative and exhaustive information on all uncertainties involved in the various situations

of exposure, their importance is acknowledged (CERRIE, 2004; ICRP, 2006, 2007; Harrisson and Day, 2008; Stabin 2008).

### 1.5.1 Sources of uncertainty

#### *1.5.1.1 Measurement*

A nuclear transition is a random process following a Poisson law. Furthermore, the counting of a radioactive sample is affected by a background resulting from natural radiation or from the activity of other radionuclides than the isotope of interest. This background is commonly assumed also to follow a Poisson law. In case of measurement of a naturally occurring radionuclide, the uncertainty on the measurement result is mostly due to the contribution of the alimentary intake.

##### 1.5.1.1.1 Decision threshold and detection limit

The total or measured number of counts $N_S$ is the sum of counts induced by background radiation $N_0$ and counts induced by the activity of interest contained in the sample (*in vitro*) or in the body (*in vivo*) (net counting) $N_n$:

$$N_S = N_0 + N_n$$

$N_0$ is determined by measuring the counts from the background in the absence of other activity. However, the background is variable and fluctuates around its mean value according to a Poisson distribution. Therefore a measured low but positive count $N_n$ may be the consequence of a mere fluctuation of the background rather than the presence of an activity of interest.

Hence a decision threshold ($DT$) is defined such that if $N_n > DT$, the sample or the body contains a radionuclide. If this decision rule is observed, a wrong decision occurs with the probability $\alpha$ that there is a sample or body contribution when, in fact, only a background effect exists (ISO, 2000). It is calculated under the hypothesis of a Poisson background, by:

$$DT = k_{1-\alpha}\sqrt{R_0\left(\frac{1}{t_0}+\frac{1}{t_S}\right)} \quad \text{(ISO, 2000)}$$

for adequate size of $R_0 t_S$ where $k_{1-\alpha}$ is the desired 1- $\alpha$ percentile of the Poisson distribution, $R_0$ the background effect counting rate, quotient of the counts $N_0$ counted during the preselected duration of the background effect measurement $t_0$, $t_S$ is the duration of the gross effect measurement. When $N_0$ is large enough (> about 30) to approximate the Poisson distribution by a normal distribution, an $\alpha$ risk of 2.5 % is obtained for $k_{1-\alpha}$ =1.96.

On the other hand, the overall variability of the counting may lead one to erroneously conclude that the radionuclide of interest is absent (β risk of false negative). A detection limit (DL) is hence defined to specify the minimum sample or body contribution which can be detected with a given probability $\beta$ of error using the measuring procedure in question. This allows a decision to be made as to whether a measuring method satisfies certain requirements and is consequently suitable for the given purpose of measurement (ISO, 2000). The DL shall refer to the smallest expectation of the net counting rate for which a wrong decision occurs with a probability $\beta$ that there is no sample contribution but only a background effect. Under assumption of Poisson background,

$$DL = (k_{1-\alpha} + k_{1-\beta})\sqrt{R_0\left(\frac{1}{t_0}+\frac{1}{t_S}\right)} \quad \text{(ISO, 2000)}$$

Typical DLs are gathered in table 1.

**Table 1 Typical detection limits (DL) for in vivo and in vitro measurements of various radionuclides (ICRP, 1997)**

| Radionuclide | Method of Measurement | | Typical DL |
|---|---|---|---|
| $^{238}$Pu | X-ray spectrometry *in vivo* | Lung | 1000 Bq |
| | Radiochemical separation and α-ray spectrometry | Urine | 1 mBq.L$^{-1}$ |
| | | Faeces | 1 mBq |
| $^{239}$Pu | X-ray spectrometry *in vivo* | Lung | 2000 Bq |
| | Radiochemical separation and α-ray spectrometry | Urine | 1 mBq.L$^{-1}$ |
| | | Faeces | 1 mBq |
| $^{241}$Am | γ-ray spectrometry *in vivo* | Lung | 20 Bq |
| | | Skeleton | 20 Bq |
| | Radiochemical separation and α-ray spectrometry | Urine | 1 mBq.L$^{-1}$ |
| | | Faeces | 1 mBq |
| $^{234}$U, $^{235}$U, $^{238}$U | γ-ray spectrometry *in vivo* | Lung | 200 Bq |
| | Radiochemical separation and α-ray spectrometry | Urine | 10 mBq.L$^{-1}$ |
| | | Faeces | 10 mBq |
| $^{137}$Cs | γ-ray spectrometry *in vivo* | Whole body | 50 Bq |
| | Radiochemical separation and α-ray spectrometry | Urine | 1 Bq.L$^{-1}$ |

#### 1.5.1.1.2 Environmental measurement

All samplers are size selective to a greater or lesser extent, under- or over-sampling at particular particle sizes, and this can result in errors in intake estimation. An investigation of the aspiration efficiency of a personal air sampler (PAS) gave values close to unity up to an aerodynamic diameter of 30 $\mu$m under workplace conditions (Mark et al, 1986). Marshall and Stevens (1980) reported that PAS: static air sampler (SAS) air concentration ratios can vary from less than 1 up to 50, depending on the nature of the work. Britcher and Strong (1994) concluded from their review of monitoring data for Magnox plant workers that intakes assessed from PAS data were about an order of magnitude greater than those implied by SAS data. The difficulties in assessing intakes from PAS measurements were considered by Whicker (2004). A large and extensive PAS monitoring programme has been ongoing since 1986 at the BNFL Sellafield nuclear fuel reprocessing site in the United Kingdom (Strong and Jones, 1989 ; Britcher and Strong 1994 ; Britcher *et al*. 1998) leading to the conclusion that the protracted use of PAS does provide a useful indicator of general environmental airborne contamination levels and a convenient means of identifying particular tasks or particular working methods which apparently give rise to localised enhanced levels of airborne contamination. However, no clear relationship was evident between significant PAS results and the evidence from biological sampling. A uranium exposure study was also conducted by Eckerman and Kerr (1999) to determine the correlation between uranium intakes predicted by PAS and intakes predicted by bioassay at the Y12 plant in Oak Ridge, USA. This study concluded that there was poor correlation between the two measurements.

#### 1.5.1.1.3 Individual measurement

For in vitro measurement, the yield of a possible chemical process is also subject to uncertainty. The calibration of detectors depends on the measurement geometry. It significantly influences the uncertainty on in vivo measurement (Toohey at al. 1991; de Carlan et al. 2007). Hurtgen and Cossonnet (2003); Lopez and Navarro (2003) conducted detailed studies of the uncertainty on in vitro and in vivo measurement, respectively.

The incorporated activities usually relate to trace quantities of the involved elements which are not excreted continuously in time but rather through stochastic processes (Usuda et al 2002). The sampling of excretion over 24 hours for urine and 72 hours for feces allows averaging this intra-individual variability. Still, a shorter sample may lead to uncertainty of orders of magnitudes on the excretion rate (Moss et al. 1969; Fig. 3).

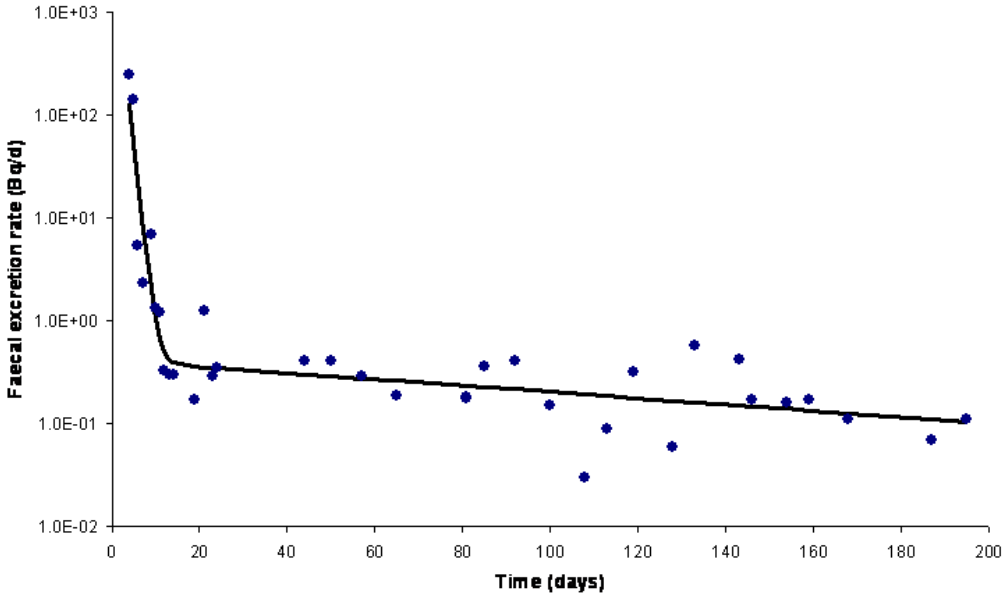



**Figure 3 Variability of faecal excretion after inhalation of $^{239}$Pu for 24 h samples (Marsh et al, 2007)**

Within the IDEAS guidelines (Doerfel *et al*, 2006) and the CONRAD project (Lopez *et al*, 2008), all these sources of uncertainty were modelled in terms of one log-normal distribution with a geometric standard deviation called scattering factor (SF). However it is acknowledged that when the activity is very low, close to the DT, the Poisson uncertainty is dominant, while it becomes negligible when the activity is high enough. Values of SF for *in vitro* measurement were determined from the follow-up of actual contamination cases with high excretion data so that Poisson variability would have little influence on the measurement (Marsh *et al*, 2007). Therefore, the determined SFs model all measurement uncertainties except Poisson variability. The suggested default SF values for various types of measurements are gathered in table 2.

**Table 2 Suggested default SF values for various types of measurements. When available, ranges are given in brackets (Doerfel et al, 2006; Marsh et al, 2008)**

| Quantity | SF |
|---|---|
| True 24 h urine | 1.1 |
| Activity concentration of $^{3}$H in urine | 1.1 |
| Simulated 24 h urine, creatinine or specific gravity normalised | 1.6 (1.3 – 1.8) |
| Spot urine sample | 2.0 |
| Faecal 24 h sample | 3 (2 – 4) |
| Faecal 72 h sample | 1.9 (1.5 – 2.2) |
| Body count (photon energy < 20 keV) | 2.3 |
| Body count (20 keV < photon energy < 100 keV) | 1.4 |
| Body count (photon energy > 100 keV) | 1.2 |

#### 1.5.1.1.4 Quality assurance

A survey of current monitoring practices within the European Union (EU) was carried out, and summarized by Rahola *et al* (2004). In many instances, there appeared to be little consensus across the EU on the optimum design of an internal dose monitoring programme for particular radionuclides and compounds (Etherington *et al*, 2004). Surveys were carried out to compile descriptions of the procedure used for *in vivo* or *in vitro* measurements, followed by recommendations on optimum parameters values and quantification of the resulting overall uncertainty on bioassay measurement (Hurtgen and Cossonnet, 2003; Génicot, 2003). For example, less than half of the laboratories reach the targeted relative uncertainty of 10 % for a 100 mBq/24 h sample and DL of 1 mBq/24 h for analysis of actinides in faeces (Etherington *et al*, 2004). Advice was provided on the choice of measurement technique, monitoring interval, required measurement sensitivity and accuracy, measurement parameters needed to achieve such performance, resulting uncertainty in assessed intakes and doses (accuracy), and minimum detectable dose (sensitivity) for individual monitoring of tritium, $^{60}$Co, radioiodine, $^{137}$Cs, uranium, plutonium and thorium. Overall, intercomparison exercises appear as a necessary tool for quality assurance of measurement facilities and process (Rahola and Falk 2000; Kramer et al. 2001; Andrasi A. 2000; Andrasi et al. 2000).

### *1.5.1.2 Model*

#### 1.5.1.2.1 Biokinetic models

Uncertainty in biokinetic models may arise because the model structure provides an oversimplified representation of the known processes, because unknown processes have been omitted from the model, or because part or all of the model formulation is based on mathematical convenience rather than consideration of processes (Leggett, 2001). As it was demonstrated for plutonium (Leggett, 2003), different mathematical modelling can agree with observed data.

##### *1.5.1.2.1.1 Source of data*

The first source of uncertainty is about the type of information used to construct the biokinetic models. These models are based on some combination of many data, coming from different sources of information. Data can come a/ directly from information on humans, i.e. quantitative measurements of the element in human subjects, b/observations of the behaviour of chemically similar elements in human subjects; c/ observations of the behaviour of the element in non-human species and d/ observations of the behaviour of chemically similar elements in non-human species (Leggett, 2001). Data types b/, c/ and d/ serve as surrogates for a/, which is the preferred type of information on which to base a biokinetic model.

The main problem is that similarities between chemically analogues elements and species do not necessarily imply similar biokinetics. Actinides have all chemical similarities together but uranium, by contrast to the other actinides, has relatively low deposition in liver, is a bone volume seeker and has a high rate of urinary excretion. Similarly, in the alkaline rare earth elements, there is a high fecal excretion of absorbed Ba and Ra but not Ca and Sr. Finally, in the group of alkali metals, K and Na are physiological opposites. K is mainly intracellular and Na is mainly extracellular (Guyton 1986). In the same way, mammals are very close all together but substantial differences in the radionuclide biokinetics may occur. As for example, Pu is rapidly lost from liver in rats, macaque monkeys and baboons, whereas is tenacious retained in hamsters, deer mice, dogs, pigs and man (Taylor 1984).

If the biokinetic model is constructed from direct human data, uncertainties in model predictions arise from limitations in the quality, completeness, and relevance of the data. In most cases, study groups are small and large inter-subject variability in the biokinetics of an element is observed. During the short observation periods, large intra-subject variability is possible. The use of unhealthy subjects whose diseases may alter the biokinetics of the element and the paucity of observations for women and children induce difficulties to interpret data. The collection of small potentially non-representative samples of tissue and inaccuracies in measurement techniques introduce measurement uncertainty. Sometimes, the exposure conditions such as the pattern or level of intake of the element are not well controlled. Finally, data may be used despite atypical study conditions and inconsistency in reported values.

#### *1.5.1.2.1.2 Absorption*

One major source of uncertainty in biokinetic models is about the assessment of the incorporation of the radionuclide. After inhalation, assumptions are made about the diameter and the physico-chemical form of the inhaled particles that determine the pulmonary deposit, the translocation to blood and therefore the distribution of the element to the organs. After ingestion, similar assessments are made about the fractional absorption from the gastrointestinal tract, that depends again on the physico-chemical properties of the radionuclide.

The uncertainty in fractional uptake from the gastrointestinal tract to blood varies considerably from one element to another. In a relative sense, uncertainties in fractional uptake are smallest for elements that are known to be nearly completely absorbed, including hydrogen (as tritium), carbon, sodium, chlorine, potassium, bromine, rubidium, molybdenum, iodine, cesium, thallium, fluorine, sulphur, and germanium. An uncertainty factor in the range 1.1-1.5 might be appropriate for each of these elements, depending on the quality and completeness of the data base for individual elements (table 3). Average uptake from the gastrointestinal tract is also reasonably well established for several frequently studied elements whose absorption is incomplete but represents at least a few percent of intake, such as copper, zinc, magnesium, technetium, arsenic, calcium, strontium, barium, radium, lead, iron, manganese, cobalt, and uranium. Uncertainty factors for these elements would also vary with the element and generally would be greater than 1.5 but no more than about 3. Relative uncertainties generally are greater for the remaining elements due to sparsity of direct observations on human subjects (e.g. ruthenium, silver), inconsistencies in reported absorption fractions (e.g. beryllium, antimony, silicon), or absorption too low to be determined with much precision under most conditions (e.g. most actinide and lanthanide elements). Absorption of a few poorly absorbed elements such as plutonium, americium, and curium has been studied under controlled conditions in human subjects, and average uptake in the adult may be known within a factor of 3 – 4 for these elements. Relative uncertainties may be greatest for several elements whose absorption has not been studied in man but for which animal data or other indirect evidence indicates absorption of at most a few hundredths of a percent, such as samarium, gadolinium, dysprosium, erbium, thulium, actinium, yttrium, and scandium. Absorption fractions for these elements are order-of-magnitude estimates.

**Table 3 ICRP values for the fractional absorption (f1) of elements from the gastrointestinal tract of adults and uncertainty factor UF (modified from Harrison et al., 2001)**

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

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

The uncertainty in intake from the lungs lies to the knowledge available for the particles considered. In absence of any relevant information, the ICRP recommend to use default parameters, which can be considered as central values. It must be pointed out that, for a given radionuclide, difference in absorption according to their chemical form may be of one order of magnitude. Any imprecision or mistake in the expert judgment may therefore lead to similar variability in the final dose. Davesne et al. (2010) determined specific values of absorption parameters for various chemical forms of Pu from *in vitro* and *in vivo* experiments and from human contamination cases. Pu dioxide, MOX may be considered as insoluble compounds, while Pu nitrate may be classified as a moderately soluble compound. Average and median estimates were calculated for $f_r$, $s_r$, and $s_s$ for each Pu compound (table 4) that could be used as central estimates of absorption for a specific chemical form, as recommended by the ICRP (2002a). Geometric standard deviations were also assessed and reveal a large variability in the parameter values.

**Table 4 Mean, median and geometric standard deviation (GSD) of $f_r$, $s_r$ and $s_s$ for Pu compounds**

| Compound | | $f_r$ | $s_r$ ($d^{-1}$) | $s_s$ ($d^{-1}$) |
|---|---|---|---|---|
| $_2$ | mean | $6.4 \times 10^{-2}$ | 3 | $1.9 \times 10^{-3}$ |
| (Type S) | median | $1.1 \times 10^{-3}$ | 1.6 | $1.0 \times 10^{-4}$ |
| | GSD | 14.3 | 4.3 | 10.7 |
| MOX | mean | $3.2 \times 10^{-2}$ | 1.1 | $3.0 \times 10^{-4}$ |
| (Type S) | median | $2.0 \times 10^{-3}$ | 0.3 | $1.0 \times 10^{-4}$ |
| | GSD | 11.2 | 3.7 | 5.0 |
| Pu nitrate | mean | $2.6 \times 10^{-1}$ | 16.7 | $5.1 \times 10^{-3}$ |
| (Type M) | median | $2.0 \times 10^{-1}$ | 11.4 | $4.0 \times 10^{-3}$ |
| | GSD | 2.7 | 11.2 | 2.3 |

#### *1.5.1.2.1.3 Transfer rates*

Uncertainties in transit times from one compartment to another may lead to substantial differences in dose assessment. A specific study on uncertainties in transit time of food has been performed in the frame of the development of the human alimentary tract model (ICRP, 2006). In that study, considering only average residence times in healthy individuals within a population, it was judged that the typical residence time of material in the mouth or oesophagus of the adult male is known within a factor of about 2. The typical residence time of material in the stomach, small intestine, right colon, left colon, or rectosigmoid colon in the

adult male is judged to be known within a factor of about 1.5. On this basis, effective dose coefficients and equivalent dose coefficients to the colon have been calculated for the examples of ingestion of $^{90}$Sr, $^{106}$Ru and $^{239}$Pu by adult males, using transit times of 8 hours and 18 hours in each of the three segments of the colon (the default value is 12 hours for each segment). In the cases of $^{90}$Sr and $^{106}$Ru the uncertainty factors for colon dose are 1.5 and 1.4 respectively, which are nearly the same as that for transit time, reflecting their close association (table 5). For $^{239}$Pu, colon dose arises solely from activity absorbed to blood, and variations in transit time have no effect on colon dose. For $^{106}$Ru the colon dose from activity in the contents makes an important contribution to effective dose, and thus the uncertainty in transit times leads to an uncertainty factor in effective dose of about 1.2. In contrast, colon doses from $^{90}$Sr and $^{239}$Pu contribute very little to effective doses and results are unchanged by variations in transit time.

**Table 5 Uncertainty Factors (UF) and ratios of dose coefficients (B/A) resulting from uncertainty in transit times in the colon, considering ingestion by adult males (from ICRP, 2006)**

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

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

#### *1.5.1.2.1.4 Inter-individual variability*

In addition to the reliability of the reference biokinetic model, the inter-individual variability should be considered when comparing the prediction of the model with the bioassay data from a given individual (table 6).

**Table 6 Examples of variability of biokinetics of radionuclides in adult humans (Leggett, 2001)**

| Study | n | Geometric mean (%) | Geometric SD | Observed maximum (%) |
|---|---|---|---|---|
| Reeve and Hesp (1976), Whole-body $^{45}$Ca retention in osteoporotic patients on day 15 post injection | 8 | 63 % | 1.2 | 85 % |
| Likhtarev *et al* (1975), $^{85}$Sr, young adult males: | | | | |
| Whole-body retention, 50 d post injection | 7 | 25 % | 1.4 | 38 % |
| Whole-body retention, 50 d post ingestion | 8 | 5.0 % | 1.6 | 10 % |
| Urinary excretion, 4 d post injection | 5 | 1.7 % | 1.2 | 2.3 % |
| Urinary excretion, 4 d post ingestion | 9 | 0.41 % | 1.6 | 0.57 % |
| Newton *et al* (1991), $^{133}$Ba, adult males: | | | | |
| Whole-body retention, 50 d post injection | 6 | 7.8 % | 1.4 | 12 % |
| Whole-body retention, 200 d post injection | 6 | 5.6 % | 1.4 | 8.9 % |
| Whole-body retention, 500 d post injection | 6 | 4.4 % | 1.4 | 7.0 % |
| Urinary excretion on d 1 post injection | 6 | 5.5 % | 1.3 | 8.2 % |
| Urinary excretion on d 5 post injection | 6 | 0.17 % | 1.9 | 0.51 % |
| Urinary excretion on d 14 post injection | 6 | 0.03 % | 2.0 | 0.10 % |

| Study | n | Geometric mean (%) | Geometric SD | Observed maximum (%) |
|---|---|---|---|---|
| ICRP Publication 20 (1973), Whole-body retention of $^{226}$Ra in Elgin patients: | | | | |
| Ages 17-23 y, 30 d post injection | 7 | 8.0 % | 1.4 | 14 % |
| Ages 17-23 y, 4-7 mo post injection | 6 | 3.1 % | 1.5 | 5.4 % |
| Ages 24-63 y, 4-7 mo post injection | 14 | 3.5 % | 1.8 | 10 % |
| Maletskos *et al* (1966), Whole-body retention of $^{224}$Ra in subjects aged 63-83 y: | | | | |
| 9-10 d post injection | 6 | 22 % | 1.2 | 28 % |
| 20 d post injection | 5 | 15 % | 1.3 | 21 % |
| Hursh *et al* (1969), Retention of $^{212}$Pb in red blood cells of adults: | | | | |
| 1 d after end of inhalation | 10 | 46 % | 1.2 | 57 % |
| 3 d after end of inhalation | 5 | 46 % | 1.3 | 60 % |
| Heard and Chamberlain (1984), Retention of $^{203}$Pb in feet of adults: | | | | |
| 1 d post injection | 4 | 1.2 % | 1.3 | 1.7 % |
| 4 d post injection | 4 | 1.1 % | 1.5 | 1.8 % |
| 10 d post injection | 4 | 1.4 % | 1.5 | 2.4 % |
| Hursh and Spoor (1973), whole-body retention in unhealthy subjects receiving uranium by injection: | | | | |
| 1 d post injection | 23 | 37 % | 1.6 | 84 % |
| 3 d post injection | 14 | 31 % | 1.7 | 77 % |
| 6 d post injection | 9 | 31 % | 1.7 | 76 % |

#### 1.5.1.2.2 Dosimetric models

The dosimetric models are based on sound principles of radiation transport but involve simplified anatomical structures and geometric considerations that also introduce uncertainty into dose estimates. Notably, the assumption of homogeneous distributions of radionuclides, target cells and dose within most tissues may be oversimplifying. Moreover, the reference person of the ICRP (ICRP, 2002b) gathers mean anatomical parameters which can be very different from the parameters of a specific individual. The NRCP (1998) considers that the uncertainties in the dosimetric models are associated with:

- incomplete information on masses, compositions, shapes and locations of the organs and tissue of the human body,
- limitations in the physical data (e.g. energy and intensity of radiations emitted by the radionuclides, photon interaction coefficients; etc.),
- limitations in computational procedures for evaluating the energy deposition of penetrating radiations,
- oversimplifications of the representations of certain complex anatomical structures in the body when calculating the energy deposition.

It evaluated the uncertainties associated with items 2 and 3 to be typically less than 20 % assuming proper application of the available data and computational methods. The uncertainties related to items 1 and 4 are typically an order-of-magnitude, although for some combination of organs and radionuclides they might be higher (NCRP, 1998). However, since 1998, the new voxel reference phantoms (ICRP, 2009) have reduced the uncertainties from items 1 and 4. Still of particular importance for short range emitters (alpha, beta and Auger) is the limited knowledge of the nature and location of target cells and distribution of radionuclides within tissues.

#### *1.5.1.2.2.1 Radionuclide location in tissues*

Dose to tissues are calculated assuming a uniform distribution of the radionuclides (sources) in the tissues. An exception is made for lungs, bone and gastrointestinal tract (ICRP 1994, 1995 and 2006). The assumption of uniform distribution is very convenient for computing purposes but is wrong in many cases. Radionuclide distribution may be heterogeneous in many tissues and even in many cells. Histological data obtained after thorium injection in hamsters showed large concentration of Th in some part of the liver cells (Brooks et al. 1985). Experimental contamination of rodents with uranium contamination leads cortical deposition and to precipitates in lung macrophages (fig. 4). Contamination with lead, beryllium and neptunium lead to similar types of deposition (Levi-Setti 1988, Berry et al. 1997, Boulhadour et al. 1997, Ceruti et al. 2002).

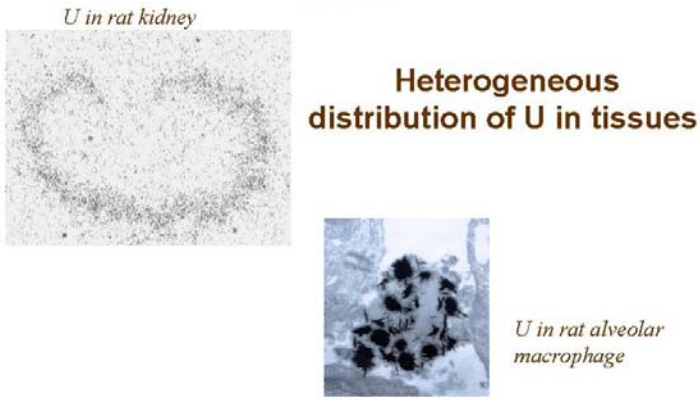



**Figure 4 Tissular and cellular distribution of uranium in some tissues (François Paquet, personal communication)**

#### *1.5.1.2.2.2 Location of target regions for cancer induction*

The position of the target cells in an organ or tissue is essential to assess the dose. In the Human Alimentary Tract Model, it is assumed that the stem cells in the bases of the crypts of the colon are the targets for cancer induction. The consequence is that, due to the depth of these targets, the alpha particles from the GI tract would not reach these cells. However, there are uncertainties both in the depth of the crypts and hence the depth of the stem cells, and whether it is only the stem cells that should be regarded as targets.

Table 7 from ICRP (2006) compares colon doses for different assumptions of target location, normalised to the default assumption that they form a continuous layer at a depth of 280 – 300 μm from the lumenal surface of the colon. Thus, uncertainties in the depth of the crypts and hence the depth of the stem cells, result in differences of about + 10% for $^{115}$Cd and smaller differences for the other examples considered. For $^{234}$U and $^{239}$Pu, there is no dose to the colon wall from activity in the lumen, and thus no change with changing assumptions regarding stem cell depth. Similarly, widening the target to include cells at higher positions up the crypts (200 – 300 μm), and thus increasing the mass of target tissue, results in a maximum change in colon dose of about 10% for $^{115}$Cd. The extreme assumption that the target may include all epithelial cells from the base of the crypts to the lumenal surface (0 – 300 μm) results in larger increase in doses. The increase by factors of about 1.5 for $^{234}$U and 3 for $^{239}$Pu are relative to the dose to the colon resulting from activity absorbed to blood. However, these increases in colon doses from $^{234}$U and $^{239}$Pu will make negligible differences to committed effective doses, which are dominated by contributions from doses to tissues and organs from activity absorbed to blood.

**Table 7 Differences (%) in equivalent dose coefficients for the colon, compared to the default case, resulting from considerations of target depth in the mucosa, considering ingestion by adult males (from ICRP, 2006)**

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

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

#### *1.5.1.2.2.3 From radiation-matter interaction to biological effects*

Absorbed dose is a quantitative measure of the exposure of tissues to ionizing radiations which can be compared with health effects observed by biological and/or epidemiological studies. The frequency of stochastic effects and the severity of deterministic effects are assumed to follow a linear relationship with dose. Its value is derived from the mean energy deposition in a define volume over a given time which results from the stochastic interaction of ionizing radiations with biological molecules. Still it does not account for the stochastic fluctuations of energy deposition at the cellular and subcellular levels, neither for the nature of the physical events and for their chemical and biological consequences. To overcome this limitation, two parallel approaches are followed: i) the classical calculation of absorbed dose in a defined volume in reproducible conditions and its adjustment to the conditions of irradiation and to the biological effect of interest through the application of a relative biological effectiveness factor (RBE) based on biological observations (ICRP, 2003); ii) the physical modelling of individual interactions, which is the field of microdosimetry (Rossi and Zaider 1991), of the induced chemical reactions and of their likely biological consequences.

For radiation protection purpose, the quantities equivalent and effective dose are used, involving radiation weighting factors $w_R$. Their values result from expert judgment on relative biological effect of radiation which is often difficult to assess from available human and animal data, while the extrapolation from *in vitro* experiments to human cancer may be questionable. Similarly, tissue weighting factors $w_T$ involve a strong simplification of the epidemiological information relative to the contribution from each type of cancer and hereditary diseases to the global detriment (ICRP, 2007).

### *1.5.1.3 Application of the models*

Uncertainties in dose calculation may arise from the misuse of the adopted models. The third European inter-comparison exercise on Internal dose assessment showed that when a same set of data is given to two different dosimetrists, different methods will be applied and therefore different numerical values will be obtained (Doerfel et al. 2003). Table 8 gives examples of differences obtained by different experts when calculating effective dose after hypothetical exposure. This table show great discrepancies between exposure, and show that the major source of uncertainties for dose assessment may arise from this latest stage.

Apart from plain mistake in the dose assessment process, the application of models requires knowing or making assumptions on the conditions of exposure. Incomplete information may therefore lead to an important uncertainty on the dose result. A major source of uncertainty is the solubility of the incorporated radionuclide (Harrison *et al*, 1998, 2001) which determines

its absorption into blood from the alimentary tract (ICRP, 2006), the respiratory tract (ICRP, 2002a) or from the wound (NCRP, 2006). Another rarely well characterized physico-chemical property is the size distribution (AMAD) of an inhaled aerosol. When the contamination is discovered as the consequence of a routine or control bioassay measurement, the time(s) of intake may be unknown while restricted to a period of potential exposure and/or to a monitoring interval. Finally, the biokinetics of an actual contamination may differ significantly from the reference model because of inter-individual variability.

**Table 8 Dose calculation performed by different experts during an intercomparison exercise (data from Doerfel et al, 2003)**

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

To limit such differences in dose assessment, the European project IDEAS proposed guidelines based on three principles (Doerfel *et al*, 2006): harmonisation (by following the guidelines any two assessors should obtain the same estimate of dose from a given data set), accuracy (the best estimate of dose should be obtained from the available data), proportionality (the effort applied to the evaluation should be proportionate to the dose – the lower the dose, the simpler the process). The application of the IDEAS guidelines were shown to result in a slight reduction of the dispersion of doses assessed for a same case (Hurtgen *et al*, 2005).

### 1.5.2 Mathematical representation

Different mathematical theories and tools are applicable to quantify uncertainty. They are representations of the knowledge of imprecise or variable quantities. These tools can be used to directly propagate uncertainty from the intake and model to the dose. Alternatively, the uncertainty on the intake and dose can be inferred from prior knowledge on uncertain quantities and from an observed measurement result by inverse propagation.

Among the available tools, probabilities are the most commonly used. In probabilistic methods, a probability density function (PDF) is selected to quantify the likelihood associated with each value of the input quantities. If dependencies between uncertain parameters are known and judged to be potentially important, then they need to be quantified. In this method, each value of the uncertainty domain is weighted by its likelihood. The direct probabilistic propagation of uncertainty consists in evaluating from this knowledge the likelihood associated with each possible result of dose and measurable quantities as PDF.

Accurate results require precise knowledge of the PDF of each uncertain parameter and of the possible correlations. Such knowledge is rarely available in practice and some information has often to be subjectively added based on expert judgment. In practical studies, some particular choices of PDF are commonly made to represent the lack of knowledge on uncertain parameters. For example, a uniform probability law is often used when no information but the extreme values is available. A triangular law is used when the extreme values and the mode are known. However subjective information may lead to less realistic results and arbitrarily change the confidence interval. Indeed, when the variability of a parameter is not well known, several different PDF could be applied and the overall

uncertainty may be underestimated by considering only one. In the same way, unknown correlations may lead to unrealistic estimation of the uncertainty.

#### *1.5.2.1 Direct propagation*

Direct propagation of uncertainty is deriving the uncertainty in consequences from known uncertainty in the causes.

##### 1.5.2.1.1 Monte-Carlo techniques

The Monte Carlo method is a numerical technique of integral calculation which converges faster than other methods in several dimensions spaces. It consists in generating a large number of random sets of input parameters according to their probability and in estimating the output of interest from discrete sums approximating the integrals to be calculated. In Monte-Carlo simulation, a physical model is applied repeatedly, using different values for each of the uncertain parameters each time. The values of each of the uncertain parameters are drawn from its PDF:

If $F(x)$ is the cumulative distribution function (CDF) of $X$, then the variable $Y = F(X)$ is uniformly distributed between 0 and 1. $n$ numbers, $r_1, r_2, \ldots, r_n$ are drawn randomly between 0 and 1. The sample of $X$ $(x_1, x_2, \ldots, x_n)$ is determined by $x_i = F^{-1}(r_i)$ where $F^{-1}$ is the inverse function of $F$. The sample of $X$ is therefore distributed according to $F(x)$. It can be used to estimate any typical statistics such as the mean or the variance and to determine the CDF of the output quantities. It follows from the law of large numbers that the mean, the standard deviation and the CDF can be calculated without knowing the PDF, using a Monte-Carlo simulation:

$$\bar{x} = \frac{1}{N}\sum_{i=1}^{N} x_i \xrightarrow[N\to+\infty]{} \mu = \int_{-\infty}^{+\infty} xP(x)dx$$

$$S^2 = \frac{\sum_{i=1}^{N}(x_i - \bar{x})^2}{N-1} \xrightarrow[N\to+\infty]{} \sigma^2 = \int_{-\infty}^{+\infty}(x-\mu)^2 P(x)dx$$

$$\frac{1}{N}\sum_{i=0,x_i\le a}^{N} x_i \xrightarrow[N\to+\infty]{} F(a) = \int_{-\infty}^{a} P(x)dx$$

The Monte-Carlo simulation is therefore a simple way to obtain useful statistics about the model outputs and can be used for complex model where no analytical solution exists. Two methods for sampling random or pseudo-random sets of number are widely used: In the Simple Random Sampling (SRS) (Cochran, 1977) method, a number between 0 and 1 is randomly drawn for each uncertain parameter to sample its CDF. In the Latin Hypercube Sampling (LHS) (McKay *et al*, 1979) method, the interval [0, 1] is first divided into sub-intervals from which numbers are randomly or deterministically drawn. This ensures that each of the uncertain parameters is represented in a fully stratified manner, no matter which component might turn out to be important.

##### 1.5.2.1.2 Examples of application in internal dosimetry

The propagation of the uncertainty on the model parameter values to the dose coefficient has been studied by Monte-Carlo techniques in several cases. Bolch *et al* (2001, 2003) assessed the uncertainties on parameter values for particle deposition and clearance in the HRTM following inhalation of a mono-dispersed aerosol. These uncertainties were propagated to the dose coefficient. Fritsch (2006) applied the same method to poly-dispersed aerosols. Farfan *et al* (2003) evaluated the uncertainties on parameters characterising source and

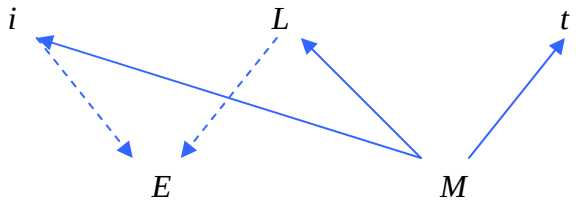
target tissues geometry in the HRTM and derived resulting uncertainties on the dose. Farfan *et al* (2005) studied uncertainty in electron absorbed fractions and lung doses from inhaled beta-emitters. Birchall and James (1994) and Marsh *et al* (2002) carried out parameter uncertainty analyses of the weighted equivalent dose to the lung per unit exposure to radon progeny respectively in a home and in a mine.

Other studies were carried out with specific radionuclides in order to assess the uncertainties on the absorption and on the systemic model. Harrison *et al* (2001) estimated the uncertainty on the fraction of activity absorbed in the gut for 14 radionuclides and observed no direct effect of it on the uncertainty in the dose coefficients. Later, the same authors studied the uncertainties on the parameters describing the systemic model for tritium in order to determine the uncertainty on the dose coefficient from intake of tritiated water and organically bound tritium (Harrison *et al*, 2002). Uncertainties in dose coefficients from ingestion of iodine and caesium were extensively studied (Dunning and Schwarz, 1981, Schwartz and Dunning, 1982, Hamby and Benke, 1999, Harvey *et al*, 2003, Apostaei and Miller, 2004). Krahenbuhl *et al* (2005) determined the uncertainty on the organ burden of Mayak workers by Monte-Carlo techniques varying the 20 excretion parameters. Bess *et al* (2007) assessed the uncertainty on the dose from plutonium inhalation as a consequence of uncertainties on the parameters of a model modified from ICRP publication to fit the data from Mayak workers. Khursheed (1998) determined the uncertainty in dose coefficients for systemic plutonium by Monte-Carlo technique considering uncertainty on the most sensitive biokinetic parameters.

Blanchardon *et al* (2007) proposed to take into account uncertainty associated with measurements and models as well as the realistic hypotheses on the conditions of exposure to estimate a distribution of possible dose values. This was performed by assuming *a priori* PDF for input data including measurement result, model parameters and conditions of exposure, and by computing the resulting PDF of dose by Monte-Carlo simulation (Molokanov and Blanchardon, 2007). However, this method did not consider the causal relationships between the different quantities. Etherington *et al* (2006) developed a method to determine the uncertainty in the dose assessments for a population of workers when default assumptions are made about model parameter values and intake patterns.

#### *1.5.2.2 Inverse propagation*

In internal dosimetry, the dose *E* and bioassay measurement *M* are consequences of the intake *i*, biokinetic and dosimetric model *L* and time of contamination *t*. However, *i*, *L* and *t* are usually not known in practice. Still, they can be inferred from observed *in vivo* and *in vitro* measurement results *M*. This process is represented in fig. 5.




$$E = i \times e_{50}(L)$$

**Figure 5 Relationships between the exposure characteristics (intake i, model L, time of contamination t) and the exposure consequences: committed effective dose E and measured activity M. The directions of the arrows indicate the propagation of information to determine i and E from M. e50(L) is the dose coefficient calculated for the model L.**

The inverse propagation of information is inferring the uncertainty in the causes from the uncertain knowledge in the consequences. The uncertainty on *M* can be propagated in the way to *i, L* and *t.* From a probabilistic point of view, the conditional probabilities of *i*, *L*, *t* and *E*, *P(i | M), P(L | M), P(t | M)* and *P(E | M)* can be inferred from the knowledge brought by the measurement result *M*. It can be calculated by applying Bayes' theorem also known as the theorem of conditional probability. Bayes' theorem is used to derive the probability of a cause knowing the probability of a consequence from a priori knowledge of the cause:

$$P(X|Y) = \frac{P(X \cap Y)}{P(Y)} = \frac{P(Y|X) \times P(X)}{P(Y)}$$

For the intake and the dose, it is:

$$P(i|M) = \frac{\int_L \int_t P(M|i,L,t) \times P(L) \times P(t) \times dL \times dt}{\int_i \int_L \int_t P(M|i,L,t) \times P(i) \times P(L) \times P(t) \times dL \times dt \times di} \times P(i),$$

$$P(E|M) = \frac{\int_L \int_t P(M|E,L,t) \times P(L) \times P(t) \times dL \times dt}{\int_i \int_L \int_t P(M|E,L,t) \times P(i) \times P(L) \times P(t) \times dL \times dt \times di} \times P(i) \text{ with } E = i \times e_{50}(L)$$

*P(i)*, *P(L)* and *P(t)* are the prior probabilities of *i*, *L* and *t*: they represent the actual or assumed knowledge on these variables before any measurement is performed. *P(M|i, L, t)* is the likelihood of the measurement given *i*, *L* and *t*: it is the probability to obtain the measurement *M* from given values of *i*, *L* and *t*. *P(i | M)* and *P(E | M)* are the posterior probabilities. They are the update of the prior probabilities by the knowledge introduced by the measurement.

#### 1.5.2.2.1 Bayesian network

A discrete Bayesian network was developed by Davesne *et al*. (2010b) to calculate the posterior probabilities of intake and dose from the measurement (fig. 6). The dose *E* is only correlated with the model *L* and with the intake *i*. The measured activity *M* is completely correlated with the bioassay quantity *S* (e.g. activity in a urine sample) but is different from it because of the counting statistics: the probability *P(M | S)* to obtain *M* given *S* is therefore modelled by a Poisson distribution of mean *S*. The bioassay quantity *S* is defined by *i*, *L* and *t*, modulated by Type B uncertainty: the probability of *S* given *i*, *L* and *t* follows a lognormal distribution of geometric mean $i \times m(L,t)$ where *m* is the retention or excretion function corresponding to the measured quantity and with a geometric standard deviation equal to a scattering factor (SF) depending on the bioassay sampling or on the *in vivo* detector calibration. Each of the six variables is discretised and the global likelihood associated to a specific intake or dose is determined by summing the likelihood obtained for each combination of the discrete values of the different variables.

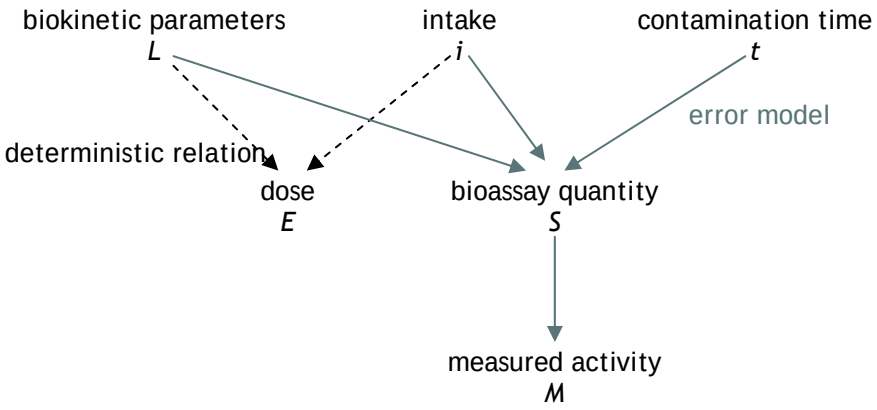



**Figure 6 Structure of the Bayesian network used to infer the posterior probabilities of intake and dose from the measured activity.**

In order to calculate the posterior probability of *i* and *E,* the first step is to evaluate the joint probability of each combination of discrete values $i_j$, $L_k$, $t_n$, $S_o$ and $E_p$:

$$P(i_j, L_k, t_n, S_o, E_p) = P(S_o | i_j, L_k, t_n) \times P(E_p | i_j, L_k) \times P(i_j) \times P(L_k) \times P(t_n) .$$

The joint probabilities of *i* and S, and *E* and *S,* and *S* alone are then calculated:

$$P(i_j, S_o) = \sum_p \sum_k \sum_n P(i_j, L_k, t_n, S_o, E_p)$$
$$P(S_o, E_p) = \sum_j \sum_k \sum_n P(i_j, L_k, t_n, S_o, E_p)$$
$$P(S_o) = \sum_p \sum_j \sum_k \sum_n P(i_j, L_k, t_n, S_o, E_p)$$

Finally, the posterior probabilities are evaluated by Bayes' theorem:

$$P(i_j | M) = \frac{\sum_o P(M | S_o) \times P(i_j, S_o)}{\sum_o P(M | S_o) \times P(S_o)}$$
$$P(E_p | M) = \frac{\sum_o P(M | S_o) \times P(S_o, E_p)}{\sum_o P(M | S_o) \times P(S_o)}$$

#### 1.5.2.2.2 WeLMoS method

The Weighted Likelihood Monte-Carlo Sampling (WeLMoS, Puncher and Birchall 2008) method is a Bayesian Monte-Carlo method which uses a weighted LHS to calculate the posterior distribution of parameter values including intake and dose. The following description is adapted from Puncher and Birchall (2008). Random samples are generated from the prior distributions of *i*, *L*, and *t* using LHS. Then a weight is assigned to each set of uncertain parameters that is equal to the likelihood of the measurement *M* given the set *i*, *L* and *t*. The weighted values are finally used to compute the posterior distributions. The WeLMoS method results in a fast and efficient.

#### 1.5.2.2.3 Markov Chain Monte-Carlo

In order to calculate posterior probabilities of intake and effective dose, Miller *et al* (1999) developed the Los Alamos UF code in which the retention/excretion functions *m* and dose coefficients $e_{50}$ for each biokinetic model *L* are tabulated. This code was developed to determine if a plutonium measurement in Los Alamos monitoring programme is positive. The posterior PDF are calculated through a Markov Chain Monte-Carlo algorithm (Miller *et al* 2002) considering up to about 200 biokinetic models to solve the above integrals. The main problem of Markov Chain Monte-Carlo is the calculation time which can be prohibitive. Puncher and Birchall (2008) showed that the WeLMoS method and the UF code obtain the same results for the same study and that the WeLMoS method is quicker.

## 1.6 Conclusion

Dosimetry in the context of internal emitters is a complex task involving measurement of activity, investigation of the conditions of exposure and application of models. The development of measurement techniques and the collection of scientific data enable internal dose assessments of increasing sensitivity, accurateness and reliability. However uncertainties do still exist at each stage of the process.

Quantifying the uncertainty on the absorbed dose to the target tissue for the health effect of interest is important for the reliability of an epidemiological study (Birchall et al 2010) or for the retrospective assessment of the individual risk. Nevertheless, this is usually not necessary in radiation protection (Harrison and Day 2008). In the frame of radiological protection, the effective dose which is compared to reference levels, dose limits and dose constraints is an indication of the exposure obtained through reference biokinetic and dosimetric models. These models and the corresponding effective dose coefficients are considered as fixed, without associated uncertainty (ICRP 2007). The assessment of intake is however specific to each situation of exposure. The propagation of uncertainty from its sources to the estimate of effective dose allows ensuring that reference or record levels, dose limits or constraints are not exceeded with a given level of confidence. In a first approach, it can be performed by comparing the current estimate with the outcome of the most penalizing hypotheses. However, more complex and accurate mathematical methods have recently been developed for application to routine monitoring of exposure (Davesne et al. 2010b) and to retrospective dose assessment (Puncher and Birchall 2008).

The harmonisation of such uncertainty assessment at the European level, its application in common situations and possible regulatory implementation represent a challenge for the years to come. Besides, the improvement of activity measurement devices (Franck 2007), biokinetic and dosimetric models (Noßke 2010) is still an on-going process. Regarding measurement, the quality assurance through the organization of intercomparisons at the European level practically appears as a key issue (Andrasi 2000). Regarding models, their complexity warrants guidance in their application (Doerfel et al. 2006), if only to remind their limitations and the unavoidable associated uncertainties. In the long term, further research is desirable to investigate the respective location of internal emitters and target regions for health effects in the human body and to link the outcome of dosimetry and microdosimetry with the observation of biological responses in the various situation of exposure.

## 1.7 Acknowledgements

I wish to thank Estelle Davesne, Lama Hadid and François Paquet for their assistance in the preparation of this manuscript and for their valuable comments.

## 1.8 References

Andrasi A. 2000 Whole-body counter intercomparison as a tool of quality assurance. Radiation Protection Dosimetry 89(3-4), 229-233.

Andrasi A., Battisti P., Castellani C.M., Tarroni G. 2000 Whole-body counter intercomparison measurements between Hungary and Italy. Radiation Protection Dosimetry 89(3-4), 247-250.

Apostoaei A I and Miller L F 2004 Uncertainties in dose coefficients from ingestion of 131I, 137Cs, and 90Sr *Health physics* 86 460-82.

Bess J D, Krahenbuhl M P, Miller S C, Slaughter D M, Khokhryakov V V, Khokhryakov V F, Suslova K G and Vostrotin V V 2007 Uncertainties analysis for the plutonium dosimetry model, doses-2005, using Mayak bioassay data *Health physics* 93 207-19.

Birchall A and James A C 1994 A rapid method for modeling the kinetics of radioactive progeny applied to thorium in the lungs *Health physics* 67 162-9.

Birchall A, Puncher M, Harrison J, Riddell A, Bailey MR, Khokryakov V, Romanov S 2010 Plutonium worker dosimetry. Radiat Environ Biophys 49(2), 203-212.

Blanchardon E, Molokanov A, Franck D, Kochetkov O, Panfilov A and Jourdain J R 2007 Estimation of the Uncertainty in Internal Dose Calculation for Two Contamination Cases *Radiation protection dosimetry*.

Bolch W E, Farfan E B, Huh C, Huston T E and Bolch W E 2001 Influences of parameter uncertainties within the ICRP 66 respiratory tract model: particle deposition *Health physics* 81 378-94.

Bolch W E, Huston T E, Farfan E B, Vernetson W G and Bolch W E 2003 Influences of parameter uncertainties within the ICRP-66 respiratory tract model: particle clearance *Health physics* 84 421-35.

Bolch W E, Eckerman K F, Sgouros G and Thomas S R 2009 MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature *J Nucl Med* 50 477-84.

Boulaud D, Gérasimo P, Martin G, Martinot L, Nourreddine A and Sens JC. 2003 Evaluation of the resuspension factor in nuclear power installations. Radioprotection 38(4), 493-508.

Boulhadour H, Paquet F, Nenot JC. 1997 Neptunium. Toxiques Nucléaires: 207-224.

Briesmeister J. 2000 MCNP - a general Monte Carlo N-particle transport code Rapport:LA-12625-M Version 4B Los Alamos National Laboratory, USA.

Britcher, A.R., Strong, R. 1994 Personal air sampling – a technique for the assessment of chronic low level exposure? Radiat. Prot. Dosim. 53, 59-62.

Britcher A.R., Battersby W.P. Peace, M.S. 1998 The practical application of models for assessing intakes of radionuclides by workers. Radiat. Prot. Dosim. 79, 71-74.

Brooks AL, Guilmette RA, Evans MJ, Diel JH. 1985 The induction of chromosome aberrations in the livers of Chinese hamsters by injected thorotrast. Strahlentherapie 80, 197-201.

Ceruti R, Ghisleni G, Ferretti E, Cammarata S, Sonzogni O, Scanziani E. 2002 Wild rats as monitors of environmental lead contamination in the urban area of Milan, Italy. Environ Pollut. 117, 255-259.

Chiavassa S, Bardiès M, Jourdain J R, Franck D 2005 OEDIPE: A Personalized Dosimetric Tool. Associating Voxel-Based Models with MCNPX. *Cancer biotherapy & radiopharmaceuticals* Volume 20, Number 3.

Cochran W 1977 Sampling techniques, Third edition *John Wiley and Sons* (New-York).

Committee Examining Radiation Risks of Internal Emitters (CERRIE) 2004 Report ISBN 0-85951-545-1.

Champion D and Peres J-M 2009 IRSN and monitoring of radioactivity in the environment in France: state and prospects. Radioprotection 44(2), 217-240.

Cristy M and Eckerman K F 1987 Specific absorbed fractions of energy at various ages from internal photon sources. I. Methods *Oak Ridge National Laboratory* Report No. ORNL/TM-8381:Vol 1.

Davesne E, Paquet F, Ansoborlo E, Blanchardon E. 2010a Absorption of plutonium compounds in the respiratory tract. J Radiol Prot. 30(1), 5-21.

Davesne E, Casanova P, Chojnacki E, Paquet F and Blanchardon E 2010b Optimisation of internal contamination monitoring programme by integration of uncertainties *Radiat Prot Dosim.*

de Carlan L, Roch P, Blanchardon E and Franck D 2007 Application of voxel phantoms in whole-body counting for the validation of calibration phantoms and the assessment of uncertainties *Radiation protection dosimetry* 125 477-82.

Doerfel H, Andrasi A, Bailey M, Berkovski V, Castellani CM, Hurtgen C, Jourdain JR, LeGuen B. 2003 Lessons learned from interlaboratory comparisons of bioassay data interpretation. Radiat Prot Dosimetry 105(1-4), 427-32.

Doerfel H, Andrasi A, Bailey M R, Berkovski V, Blanchardon E, Castellani C M, Hurtgen C, Le Guen B, Malatova I, Marsh J W and Stather J 2006 General guidelines for the estimation of committed effective dose from incorporation monitoring data (Project IDEAS - EU Contract No. FIKR-CT2001-00160) *Research Center Karlsruhe* (Karlsruhe) Research report FZKA 6457, ISSN 0947-8620.

Dunning D E, Jr. and Schwarz G 1981 Variability of human thyroid characteristics and estimates of dose from ingested $^{131}$I *Health physics* 40 661-75.

Eckerman K.F and Kerr G.D. 1999. Y12 uranium exposure study. Oak Ridge, TN: Oak Ridge National laboratory ORNL/TM-1999-114.

Etherington G, Cossonnet C, Franck D, Génicot J L, Hurtgen C, Jourdain J R, Le Guen B, Rahola T, Sovijärvi J, Stradling G N, Ansoborlo E and Bérard P 2004 Optimisation of Monitoring for Internal Exposure (OMINEX), Report NRPB-W60 *National Radiological Protection Board* (Chilton) W60.

Etherington G, Birchall A, Puncher M, Molokanov A and Blanchardon E 2006 Uncertainties in doses from intakes of radionuclides assessed from monitoring measurements *Radiation protection dosimetry* 121 40-51.

Farfan E B, Huston T E, Bolch W E, Vernetson W G and Bolch W E 2003 Influences of parameter uncertainties within the ICRP-66 respiratory tract model: regional tissue doses for $^{239}$PuO2 and $^{238}$UO2/$^{238}U_3O_8$ *Health physics* 84 436-50.

Farfan E B, Bolch W E, Huston T E, Rajon D A, Huh C and Bolch W E 2005 Uncertainties in electron-absorbed fractions and lung doses from inhaled beta-emitters *Health physics* 88 37-47.

Franck D 2007 Potential of modern technologies for improving internal exposure monitoring. Radiat Prot Dosimetry 127(1-4), 233-2399.

Fritsch P 2006 Uncertainties in aerosol deposition within the respiratory tract using the ICRP 66 model: a study in workers *Health physics* 90 114-26.

Geant4 Collaboration (Agostinelli et al.) 2004 Geant4 – a simulation toolkit. Nuclear Instruments and Methods in Physics Research, A506, 250–303.

Génicot J L 2003 OMINEX Work Package 3, Uncertainties on *in vivo* measurements - A survey of European laboratories, Scientific Report SCK•CEN - BLG-943 *SCK•CEN* (Mol) BLG-943.

Guyton AC. 1986 Human physiology and mechanisms of disease. Philadelphia, PA: W.B. Saunders.

Hamby D M and Benke R R 1999 Uncertainty of the iodine-131 ingestion dose conversion factor *Radiation protection dosimetry* 82 245-56.

Harrison J D, Khursheed A, Phipps A W, Goossens L, Kraan B and Harper F 1998 Uncertainties in biokinetic parameters and dose coefficients determined by expert judgement *Radiat Prot Dos* 79 355-8.

Harrison JD, Leggett RW, Nosske D, Paquet F, Phipps AW, Taylor DM, Métivier H. 2001 Reliability of the ICRP's dose coefficients for the members of the public. II. Uncertainties in the absorption of ingested radionuclides and the effect on dose estimates. Radiat. Prot. Dosim. 95, 295-308.

Harrison J D, Khursheed A and Lambert B E 2002 Uncertainties in dose coefficients for intakes of tritiated water and organically bound forms of tritium by members of the public *Radiation protection dosimetry* 98 299-311.

Harrison J, Day P. 2008 Radiation doses and risks from internal emitters. J Radiol Prot. 28(2):137-59.

Harvey R P, Hamby D M and Benke R R 2003 Age-specific uncertainty of the $^{131}$I ingestion dose conversion factor *Health physics* 84 334-43.

Heard M J and Chamberlain A C 1984 Uptake of Pb by human skeleton and comparative metabolism of Pb and alkaline earth elements *Health physics* 47 857-65.

Hendricks J.S., McKinney G.W., Fensin M.L., James M.R., Johns R.C., Durkee J.W., Finch J.P., Pelowitz D.B., Waters L.S., Johnson M.W. 2008 MCNPX 2.6.0 Extensions Rapport: LA-UR-08-2216, Los Alamos National Laboratory, USA.

Hursh J B, Schraub A, Sattler E L and Hofmann H P 1969 Fate of $^{212}$Pb inhaled by human subjects *Health physics* 16 257-67.

Hursh J B and Spoor N L 1973 Data on man *Handbook of Experimental Pharmacology* 36 197-239.

Hurtgen C and Cossonnet C 2003 OMINEX Work Package 3, Uncertainties on bioassay measurements, Scientific Report SCK•CEN - BLG-935 *SCK•CEN* (Mol) BLG-935.

Hurtgen C, Andrasi A, Bailey M R, Birchall A, Blanchardon E, Berkovski V, Castellani C M, Cruz-Suarez R, Davis K, Doerfel H, LeGuen B, Malatova I, Marsh J and Zeger J 2005 Intercomparison exercise on Internal Dose Assessment performed jointly by the International Atomic Energy Agency and the IDEAS project (“General Guidelines for the Evaluation of Incorporation Monitoring Data”, carried out within the 5th EU Framework Programme) - Scientific report SCK•CEN-BLG-1018 *SCK•CEN* (Mol) SCK•CEN-BLG-1018.

IAEA 1999 Assessment of occupational exposure due to intakes of radionuclides *IAEA* (Vienna) Safety Series n° RS-G-1.2.

International Commission on Radiological Protection 1973 Alkaline earth metabolism in adult man. ICRP Publication 20 volume 20 (Oxford: Pergamon Press).

International Commission on Radiological Protection 1993 Age-dependent doses to member of public from intake of radionuclides: Part 2 Ingestion dose coefficients. ICRP Publication 67 *Annals of the ICRP* 23(3/4) (Oxford: Elsevier Science Ltd).

International Commission on Radiological Protection 1994a Human respiratory tract model for radiological protection. ICRP Publication 66 *Annals of the ICRP* 24(1-3) (Oxford: Elsevier Science Ltd).

International Commission on Radiological Protection 1995b Basic anatomical and physiological data: The skeleton. ICRP Publication 70 *Annals of the ICRP* 25(2) (Oxford: Elsevier Science Ltd).

International Commission on Radiological Protection 1997 Individual monitoring for internal exposure of workers. ICRP Publication 78 *Annals of the ICRP* 27(3/4) (Oxford: Elsevier Science Ltd).

International Commission on Radiological Protection 1998 CD-ROM Version 2.01: The ICRP database of dose coefficients: workers and members of the public: An extension of ICRP publications 68 and 72.

International Commission on Radiological Protection 2002a Guide for practical application of the ICRP Human Respiratory Tract Model. Supporting guidance 3 *Annals of the ICRP* 32(1-2) (Oxford: Elsevier Science Ltd).

International Commission on Radiological Protection 2002b Basic anatomical and physiological data for use in radiological protection: reference values. ICRP Publication 89 *Annals of the ICRP* 32(3/4) (New York: Elsevier).

International Commission on Radiological Protection 2003. Relative Biological Effectiveness, Radiation Weighting and Quality Factor. ICRP Publication 92. Annals of the ICRP 33(4) (Oxford: Elsevier Ltd).

International Commission on Radiological Protection 2006 Human alimentary tract model for radiological protection. ICRP Publication 100 Annals of the ICRP 36(1-2) (Oxford: Elsevier Ltd).

International Commission on Radiological Protection 2007 The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103 *Annals of the ICRP* 37(2-4) (Oxford: Elsevier).

International Commission on Radiological Protection 2008 Nuclear Decay Data for Dosimetric Calculations. ICRP Publication 107 *Annals of the ICRP* 38(3) (Oxford: Elsevier).

International Commission on Radiological Protection 2009 Adult reference computational phantoms. ICRP Publication 110 *Annals of the ICRP* 39(2) (Oxford: Elsevier).

International Organization for Standardization 2000 Determination of the detection limit and decision threshold for ionizing radiation measurements -- Part 1: Fundamentals and application to counting measurements without the influence of sample treatment ISO 11929-1:2000.

International Organization for Standardization 2001 Radiation protection - Performance criteria for radiobioassay - Part 1: General principles ISO 12790-1:2001.

International Organization for Standardization 2006 Radiation protection - Monitoring of workers occupationally exposed to a risk of internal contamination with radioactive material ISO 20553:2006(E).

Kawrakow I., Rogers D.W.O. 2001 The EGSnrc Code System: Monte Carlo Simulation of Electron and Photon Transport. NRCC Report PIRS-701.

Krahenbuhl M P, Bess J D, Wilde J L, Vostrotin V V, Suslova K G, Khokhryakov V F, Slaughter D M and Miller S C 2005 Uncertainties analysis of doses resulting from chronic inhalation of plutonium at the Mayak production association *Health physics* 89 33-45.

Kramer G.H., Loesch R.M., Olsen P.C. 2001 The second international in-vivo monitoring intercomparison program for whole body counting facilities by Canadian and United States agencies. Health Physics 80(3), 214-224.

Khursheed A 1998 Uncertainties in dose coefficients for systemic plutonium Radiat Prot Dos 78 121-6.

Leggett R W 2001 Reliability of the ICRP's dose coefficients for members of the public. 1. Sources of uncertainty in the biokinetic models. Radiat Prot Dosimetry 95(3), 199-213.

Leggett R W 2003 Reliability of the ICRP's dose coefficients for members of the public. III. Plutonium as a case study of uncertainties in the systemic biokinetics of radionuclides *Radiation protection dosimetry* 106 103-20.

Leggett R W, Eckerman K F, Khokhryakov V F, Suslova K G, Krahenbuhl M P and Miller S C 2005 Mayak worker study: an improved biokinetic model for reconstructing doses from internally deposited plutonium *Radiation research* 164 111-22.

Levi-Setti R. 1988 Structural and microanalytical imaging of biological materials by scanning microscopy with heavy-ion probes. Annu Rev Biophys Biophys Chem 17, 325-47.

Likhtarev I A, Dobroskok I A, Ilyin L A, Krasnoschekova G P, Likhtareva M, Smirnov B I, Sobolev E P, Shamov V P and Shapiro E L 1975 A study of certain characteristics of strontium metabolism in a homogeneous group of human subjects *Health physics* 28 49-60.

Lopez M A and Navarro T 2003 Sensitivity of a low energy Ge detector system for in vivo monitoring in the framework of ICRP 78 applications *Radiation protection dosimetry* 105 477-82.

Lopez M A, Etherington G, Castellani C M, Franck D, Hurtgen C, Marsh J W, Nosske D, Breustedt B, Blanchardon E, Andrasi A, Bailey M R, Balashazy I, Battisti P, Berard P, Birchall A, Broggio D, Challeton-de-Vathaire C, Cruz-Suarez R, Doerfel H, Giussani A, Hodgson A, Koukouliou V, Kramer G H, Le Guen B, Luciani A, Malatova I, Molokanov A, Moraleda M, Muikku M, Oeh U, Puncher M, Rahola T, Stradling N and Vrba T 2008 Internal dosimetry: towards harmonisation and coordination of research *Radiation protection dosimetry* 131 28-33.

Maletskos C J, Keane A T, Telles N C and Evans R D 1966 The Metabolism of Intravenously Administered Radium and Thorium in Human Beings and the Relative Absorption from the Human Gastrointestinal Tract of Radium and Thorium in Simulated Radium Dial Paints *Radium and Mesothorium Poisoning Dosimetry and Instrumentation Techniques in Applied Radioactivity* 202-317.

Mark, D., Vincent, J.H., Stevens, D.C., et al. 1986 Investigation of the entry characteristics of dust samplers of a type used in the British nuclear industry. Atmospheric Environ. 20, 2389–2396.

Marsh J W, Birchall A, Butterweck G, Dorrian M D, Huet C, Ortega X, Reineking A, Tymen G, Schuler C, Vargas A, Vezzu G and Wendt J 2002 Uncertainty analysis of the weighted equivalent lung dose per unit exposure to radon progeny in the home *Radiation protection dosimetry* 102 229-48.

Marsh J W, Blanchardon E, Castellani C M, Desai A D, Dorrian M D, Hurtgen C, Koukouliou V, Lopez M A, Luciani A, Puncher M, Andrasi A, Bailey M R, Berkovski V, Birchall A, Bonchug Y, Doerfel H, Malatova I, Molokanov A and Ratia H 2007 Evaluation of scattering factor values for internal dose assessment following the IDEAS guidelines: preliminary results *Radiation protection dosimetry* 127 339-42.

Marsh J W, Castellani C M, Hurtgen C, Lopez M A, Andrasi A, Bailey M R, Birchall A, Blanchardon E, Desai A D, Dorrian M D, Doerfel H, Koukouliou V, Luciani A, Malatova I, Molokanov A, Puncher M and Vrba T 2008 Internal dose assessments: uncertainty studies and update of ideas guidelines and databases within CONRAD project *Radiation protection dosimetry* 131 34-9.

Marshall, M., Stevens, D.C. 1980 The purposes, methods and accuracy of sampling for airborne particulate radioactive materials. Health Phys. 39, 409–423.

McKay M D, Beckman R J and Conover W J 1979 Comparison of three methods for selecting values of input variables in the analysis of output from a computer code *Technometrics* 21 239-45.

Miller G, Inkret W C and Martz H F 1999 Internal dosimetry intake estimation using Bayesian methods *Radiation protection dosimetry* 82 5-17.

Miller G, Martz H F, Little T T and Guilmette R 2002 Bayesian internal dosimetry calculations using Markov Chain Monte Carlo *Radiation protection dosimetry* 98 191-8.

Molokanov A and Blanchardon E 2007 Dependence of the Dose Estimate on the Time Pattern of Intake by the Example of Tritiated Water Intakes *Radiation protection dosimetry* 127 387-91.

Moss W D, Campbell E E, Schulte H F and Tietjen G L 1969 A study of the variations found in plutonium urinary data *Health physics* 17 571-8.

National Council on Radiation Protection and Measurements 1998 Evaluating the reliability of biokinetic and dosimetric models and parameters used to assess individual doses for risk assessment purposes. NCRP commentary No. 15 (Bethesda: NCRP).

National Council on Radiation Protection and Measurements 2006 Development of a biokinetic model for radionuclide-contaminated wounds and procedures for their assessment, dosimetry and treatment. NCRP Report No. 156 (Bethesda: NCRP).

Pafundi D., Rajon D., Jokisch D., Lee C. and Bolch W. E. 2010 An image-based skeletal dosimetry model for the ICRP reference newborn—internal electron sources. Phys. Med. Biol. 55, 1785–1814.

Nelson WR, Hirayama H, Rogers DWO 1985 The EGS4 Code System. http://www.slac.stanford.edu/pubs/slacreports/slac-r-265.html.

Newton D, Harrison G E, Kang C and Warner A J 1991 Metabolism of injected barium in six healthy men *Health physics* 61 191-201.

Noßke D, Blanchardon E, Bolch WE, Breustedt B, Eckerman KF, Giussani A, Harrison JD, Klein W, Leggett RW, Lopez MA, Luciani A, Zankl M 2010 New developments in internal dosimetry models. Radiat Prot Dosimetry.

Puncher M and Birchall A 2008 A Monte Carlo method for calculating Bayesian uncertainties in internal dosimetry *Radiation protection dosimetry* 132 1-12.

Rahola T., Falk R. 2000 Whole-body measurement and quality assurance. Radiation Protection Dosimetry 89(3-4), 243-245.

Rahola T, Etherington G, Bérard P, Le Guen B, Hurtgen C, Muikku M and Pusa S 2004 Survey of internal dose monitoring programmes for radiation workers, Report STUK-A203 *STUK* (Helsinki) A203.

Reeve J and Hesp R 1976 A model-independent comparison of the rates of uptake and short term retention of $^{47}$Ca and $^{85}$Sr by the skeleton *Calcified tissue research* 22 183-9.

Rossi H., Zaider M. 1991 Elements of microdosimetry. Med. Phys. 18(6), 1085-1092.

Salvat F., Fernández-Varea J.M., Sempau J. 2006 PENELOPE-2006: A Code System for Monte Carlo Simulation of Electron and Photon Transport. Workshop Proceedings Barcelona, Spain 4-7 July 2006.

Schwarz G and Dunning D E, Jr. 1982 Imprecision in estimates of dose from ingested $^{137}$Cs due to variability in human biological characteristics *Health physics* 43 631-45.

Stabin MG. 2008 Uncertainties in internal dose calculations for radiopharmaceuticals. J Nucl Med. 49(5), 853-60.

Strong R. and Jones S.R. 1989 A review of the development and application of a plutonium urinary excretion model at the nuclear fuel processing site of British Nuclear Fuels plc. Radiat. Prot. Dosim. 26, 141-144.

Taylor DM. 1984 The retention of plutonium and americium in liver: an interspecies comparison. Radiation-Risk-Protection 1, 431-434.

Toohey R, Palmer E, Anderson L, Berger C, Cohen N, Eisele G, Wachholz B and Burr W, Jr. 1991 Current status of whole-body counting as a means to detect and quantify previous exposures to radioactive materials. Whole-body Counting Working Group *Health physics* 60 Suppl 1 7-42.

Usuda K, Kono K, Dote T, Shimizu H, Tominaga M, Koizumi C, Nakase E, Toshina Y, Iwai J, Kawasaki T and Akashi M 2002 Log-normal distribution of the trace element data results from a mixture of stochastic input and deterministic internal dynamics *Biological trace element research* 86 45-54.

Wätjen U., Szanto Zs, Altzitzoglou T., Sibbens G., Keightle J., Van Ammel R., Hult M., De Cort M. 2007. Evaluation of EC measurement comparison on simulated airborne particulates $^{137}$Cs in air filters. Report EUR 22926 EN, ISBN 978-92-79-06962-8.

Wätjen, U., Spasova, Y., Altzitzoglou, T. Measurement comparisons of radioactivity among European monitoring laboratories for the environment and food stuff. 2008a. Applied Radiation and Isotopes 66(6-7), 742-749.

Wätjen U., Spasova Y., Altzitzoglou T., Emteborg H., Pommé S. 2008b. Evaluation of EC measurement comparison for $^{137}$Cs, $^{40}$K and $^{90}$Sr in milk powder. Report EUR23270 EN, ISBN 978-92-79-08500-0.

Whicker J.L. 2004. Relationship of air sampling measurements to internal dose: a review. Midyear Health Physics Society Meeting, 73-77.

# 2 THE ISSUE OF RISK ESTIMATION IN THE CONTEXT OF INTERNAL EMITTERS – MISUSES OF EQUIVALENT AND EFFECTIVE DOSE

**John Harrison**

***Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, United Kingdom***

*Abstract*

*There are extensive data on the risks of disease, principally cancer, following exposures to external radiation but less information on risks from internal emitters, radionuclides retained in body organs and tissues following their inhalation or ingestion. The principal source of information on radiation risks that informs international standards is the follow-up studies of the survivors of the atomic bombings at Hiroshima and Nagasaki. The risk estimates derived for the A bomb survivors relates to high dose rate exposures to gamma rays. Studies of protracted external exposures of radiation worker cohorts are of critical importance in determining the applicability of these dose estimates at low doses and dose rates. The latest analysis of the UK National Registry for Radiation Workers established a dose-response relationship for cancer consistent with the linear extrapolation of A bomb risk factors to low doses.*

*In the ICRP protection system, the risk estimates derived from the A bomb survivor studies are applied to all radiation exposures including those from internal emitters. While external exposures generally result in fairly uniform exposures of body tissues, doses from internal emitters include protracted heterogeneous exposures to short-range emissions of alpha particles and low energy electrons (e.g. from plutonium-239 and tritium). Risk estimates for internal emitters that allow comparisons include lung cancer caused by radon and plutonium-239, liver cancer and leukaemia in patients given 'Thorotrast', and bone cancer from radium. The available epidemiological data on effects of internal emitters provide support the assumptions of equivalence between internal and external exposures, taking account of difference due to radiation quality. This equivalence is also supported in general by animal data and mechanistic studies. However, substantial uncertainties remain and the adequacy of protection for internal emitters continues to be questioned. A research priority must be the pursuance of all possible sources of additional epidemiological data.*

*A distinction should be drawn between the scientific basis of radiation protection and the application of science in the development of a practical system of protection. Effective dose is used in the ICRP protection system as a risk-related quantity for the control of sources and radiation exposures. The calculation of effective dose to a sex-averaged reference person involves simplifying assumptions, particularly in the choice of radiation and tissues weighting factors. It enables all radiation exposures to be summed in a single quantity for comparison with dose limits, constraints and reference levels for workers or members of the public, but it does not provide best estimates of dose and risk to individuals. However, the biokinetic and dosimetric models developed by ICRP for the calculation of organ and tissue doses from internal emitters are becoming increasingly physiologically realistic. As well as improving the reliability of calculations of effective dose, these models are well suited for adaptation to scientific applications, including the calculation of doses to individuals in epidemiological studies. An important development in this respect is the consideration of uncertainties in dose estimates.*

## 2.1 Introduction

People are exposed to radiation from external sources and from radionuclides incorporated into the body following their inhalation or ingestion, so-called internal emitters. There are extensive data on the risk of disease, principally cancer, following exposures to external radiation but less information on risks from internal emitters. The scientific data are regularly reviewed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and others including the Biological Effects of Ionising Radiation (BEIR) Committee of the US National Academy of Sciences. The system of protection devised by the International Commission on Radiological Protection (ICRP) is based on the available scientific evidence and particularly the reviews of UNSCEAR as well as analyses undertaken by ICRP committees. ICRP issued new recommendations in 2007 (ICRP 2007) that took account of the most recent analyses of epidemiological data, principally the follow-up studies of the survivors of the atomic bombings at Hiroshima and Nagasaki (UNSCEAR 2000, 2008, NAS/NRC 2006, Preston 2003, Preston et al 2007). The risk estimates derived for the A bomb survivors relate to external gamma radiation. In the ICRP protection system, these risk estimates are applied also to doses and risks from internal emitters despite these including protracted heterogeneous exposures to short range emissions of alpha particles and low energy beta particles. An important question, therefore, is what evidence is available in support of this approach.

Radiation doses from intakes of radionuclides are estimated using biokinetic and dosimetric models (ICRP 1991, 2007, CERRIE 2004, Harrison and Day 2008). Biokinetic models are mathematical representations of the movement of elements and their radioisotopes within the body and their uptake and retention in organs and tissues. They are used to calculate the number of radioactive disintegrations occurring in individual organs and tissues. Dosimetric models represent the geometrical relationships of body structures and are used to calculate energy deposition and hence dose in so-called “target regions” (organs and tissues) per disintegration occurring in “source regions”. ICRP is the internationally recognised source of such models. ICRP models consider intakes of radionuclides by ingestion and inhalation, taking account of doses to the alimentary and respiratory tracts as well as to other organs and tissues following absorption to blood (ICRP 1994a, 1996). Doses are calculated for adults, for children of different ages, and for in utero irradiation of the embryo and fetus (ICRP 1996, 2001).

The biokinetic and dosimetric models developed by ICRP are used in the calculation of equivalent and effective dose coefficients for use in the recommended protection system (ICRP, 1991, 2007). However, the models are also used in the calculation of doses for other purposes, including epidemiological studies and calculations of probability of cancer causation (Harrison and Day, 2008). It is important to distinguish, therefore, between the application of science in the calculation of effective dose coefficients, which involves simplifying assumptions, and the use of best estimates of dose and risk, often with estimates of associated uncertainties.

Simplifying assumptions made in the calculation of equivalent and effective dose include the use of radiation and tissue weighting factors and reliance on a linear non-threshold (LNT) dose response relationship for the induction of cancer and hereditary effects at low doses. Radiation weighting factors ($w_R$) are used to represent differences between radiation types in their ability to cause cancer per unit absorbed dose (Gy) but they do not attempt to represent all known differences between radiation types and energies for different tissues and cancer types (ICRP 2007, Harrison and Day 2008). Similarly, a single set of tissue weighting factors ($w_T$) is used to represent the contributions of doses to individual organs and tissues to the overall risk of cancer and hereditary effects (ICRP 1991, 2007). These $w_T$ values are chosen as averaged and rounded values on the basis of age- and sex- specific risk data. The application of an LNT dose response relationship is implicit in the addition of doses from different radionuclides delivering doses over different time periods to different organs and

tissues. The purpose of these calculations is not to provide an accurate measure of dose and risk to an individual but to provide a single quantity that can be used in the control of exposures, relating to reference persons.

Although the biokinetic and dosimetric models published by ICRP are intended primarily for the calculation of equivalent and effective doses, they also provide a good starting point for studies requiring the calculation of doses to individuals or specific population groups. An example of current importance is the estimation of doses to workers at the Russian Mayak plutonium plant and to people living near the Techa River which was heavily contaminated by radionuclide discharges from the Mayak plant (Shagina *et al* 2007, Sokolnikov *et al* 2008, Harrison 2009). Epidemiological studies of health effects in these population groups require best estimates of absorbed doses to organs and tissues (measured in Gy), taking account of the specific circumstances of exposure.

While there are uncertainties in all aspects of the calculation of doses and risks from internal emitters, ICRP dose coefficients are published as single values without consideration of uncertainties (ICRP 2007, Harrison and Day 2008). The control of exposures relies on the principles of optimisation of protection, using constraints and reference levels. Since equivalent and effective doses are not calculated as best estimates for specific individuals or groups, they are not amenable to direct quantification of uncertainties. However, an understanding of sources of uncertainty and their magnitude can be helpful in determining the adequacy of protection. It is clear that consideration of uncertainties is appropriate when considering estimates of organ doses in epidemiological studies or calculations of probability of cancer causation.

This review provides a brief outline of information on radiation risks, comparing cancer risk estimates for exposures to external sources with more limited data on risks from internal emitters. The use of biokinetic and dosimetric models by ICRP in the calculation of equivalent and effective doses for protection purposes is explained in the context of developments resulting from the new ICRP (2007) recommendations. A distinction is drawn between the adequacy of the ICRP calculations of effective dose to reference persons for the purposes of planning and regulatory control, and the calculation of best estimates of dose and risk to individuals. Research priorities are considered in relation to the improvement of dose calculations and risk estimates for internal emitters. Examples are given of the improvement of risk estimates for plutonium-239 inhalation by Mayak workers and chronic *in utero* exposures to strontium-90 and other radionuclides resulting from discharges to the Techa River. Requirements for the consideration of uncertainties are also briefly addressed.

## 2.2 Risks from radiation exposure

### 2.2.1 Cancer risks from external radiation

Risk estimates for radiation-induced cancers are largely derived from studies of the effects of external radiation, the principal source of information being long-term studies of those who survived the immediate effects of the atomic weapons' explosions at Hiroshima and Nagasaki in 1945 (A bomb survivors). The cancer incidence and mortality data for A-bomb survivors show a statistically significant increase in solid cancers at doses from around 100 mGy up to around 3 Gy (UNSCEAR 2000, Preston 2003, Preston et al 2007). The data on solid cancer incidence indicate that any dose threshold (i.e. below which risks are not increased) would not exceed 85 mGy (Preston et al 2007). There is good evidence from these studies for increased risks of all solid cancers as a group and of leukaemia from external exposures and to a lesser degree of certainty for a range of specific solid cancers e.g. stomach, colon, lung, liver and bone. The specific risk estimates per unit dose vary between solid cancer types and have wider confidence intervals than for all solid cancers combined. Over the last few decades cancer survival has been increasing rapidly and the

emphasis for risk estimation has moved from calculating mortality risk to incidence risk. This quantification of cancer rates avoids the problem that cause of death information may not record cancer that is not considered to have been a contributory cause. The latest risk estimates from the A bomb survivor studies are predominantly based on incidence data.

In the ICRP (1991, 2007) protection system, the risk estimates derived from the A bomb survivor studies are applied to all radiation exposures. The extrapolation to lower doses and dose rates of external radiation require assumptions regarding dose response relationships (see below). Epidemiological studies of radiation effects following radiation exposure at low doses and dose rates, as in occupational situations, are valuable in determining the validity of these assumptions. In addition, an important question is the applicability of risk estimates derived for external exposure to doses received from radionuclides incorporated into the body following their inhalation or ingestion, so-called internal emitters. While external exposures generally result in fairly uniform exposures of body tissues, doses from internal emitters include protracted heterogeneous exposures to short range emissions of alpha particles and low energy beta particles (eg. from plutonium-239 and tritium). Direct epidemiological evidence of risks from internal emitters is valuable in determining the validity and hence reliability of the assumptions made for radiation protection purposes.

In applying the risk estimates derived from the A-bomb survivor data to cancer risks at low doses and dose rates, ICRP use an empirical correction factor, the Dose and Dose Rate Effectiveness Factor (DDREF), assuming a value of two for solid cancers (ICRP 1991, 2007). This assumption that risks per unit dose are lower at lower doses and dose rates is based largely on animal and in vitro data showing curvilinear dose-response relationships for acute exposures to gamma rays and x-rays. For leukaemia, the A-bomb survivor data are consistent with the use of a linear quadratic dose–response relationship – in line with a reduction in the risk per unit dose by a factor of 2 at low doses - and no additional correction is applied for low dose rates. The US BEIR Committee (NAS/NRC 2006) undertook probabilistic analyses of dose response data from epidemiological and experimental studies and obtained a modal value for DDREF of 1.5. However, judgements on an appropriate value for DDREF depend on the weight given to different sources of data. On the basis of the A-bomb survivor data, it is not possible to distinguish between a DDREF of 1 (no DDREF) or 2 for solid cancers (UNSCEAR 2000, Preston et al 2003). In addition, other epidemiological studies do not provide direct support for reduced effectiveness of radiation at low dose rates although uncertainties in these data do not allow a firm judgement on DDREF values (UNSCEAR 2000, 2011).

The third analysis of the UK National Registry for Radiation Workers (NRRW) examined cancer risks in this very large cohort of workers exposed to low doses of radiation over many years (Muirhead et al 2009). Although overall, the analysis showed lower cancer rates than in a normal population (healthy worker effect), a dose-response relationship was established consistent with the linear extrapolation of A-bomb risk factors to low doses with no DDREF applied. The third analysis of the NRRW had follow-up to 2001, and was based on over 174,000 workers with an average lifetime dose of 25 mSv. The total follow-up was almost 4 million person-years and of the 26,731 deaths examined in the analysis of external radiation exposures, 8107 were attributed to cancers. The A bomb survivor studies have similar person-years follow-up but twice the number of deaths. The estimates of relative risk, in relation to external doses, from the third analysis of the NRRW for ‘all solid cancers’ and leukaemia were in good agreement with those of the A bomb survivor studies but with far larger confidence intervals which are in part the result of the NRRW having only half the number of deaths and in part due to lower lifetime doses among NRRW participants. There was some evidence of increased risks of specific cancers but the study still lacked sufficient statistical powers to reliably identify specific risks.

Based largely on the A-bomb survivor data and an assumed DDREF of two, ICRP (2007) use a nominal risk coefficient of 5% per Sv for radiation-induced fatal cancer in a population exposed to low doses and dose rates and further assume a linear non-threshold (LNT) dose

response relationship. It is the consensus view that LNT is the best approach on current evidence for radiation protection purposes on the basis of experimental data and our understanding of the biological mechanisms involved in the initiation and development of cancer (Preston 2003, NCRP 2001, ICRP 2007, HPA 2009). The LNT assumption is essential for the operation of the current protection system, allowing the addition of external and internal doses of different magnitudes, with different temporal and spatial patterns of delivery. However, the LNT dose response remains controversial and the shape of the dose-response curve at low doses is an active area of research involving European and international collaboration (Tubiana et al, 2008; Feinendegen et al, 2008; Allison, 2009).

Studies of protracted external exposures in worker cohorts are of critical importance in providing information on the shape of dose – response relationships for cancer, whether DDREF should be used for protection purposes, and the validity of the LNT dose-response assumption at low doses and dose rates.

### 2.2.2 Cancer risks from internal emitters

An important question is whether the risk factors derived from studies of the A-bomb survivors can be applied generally. As explained above, these risk factors, which apply to short, homogeneous, high external doses of gamma radiation at a high dose rate, are applied by ICRP in all situations, including heterogeneous, low dose exposures to charged particles at low dose rates over protracted time periods. This question is relevant to internal exposures to alpha particle emitting radionuclides since alpha particles only travel very short distances (a few tens of microns) in tissue. Low energy beta particles also travel short distances in body tissues; for example, the 5.7 keV (average) electrons emitted during beta decay of tritium have a mean track length of 0.56 micrometres (μm), small compared with typical cell diameters of 10 – 20 μm.

In relation to the application of external risk factors to internal exposure to alpha particle irradiation, a number of human studies (UNSCEAR 2000, 2011, WHO 2001) provide information that has been used by ICRP (1991) and others to estimate risks of liver, bone and lung cancer. Liver cancer excesses were observed in patients given intravascular injections of 'Thorotrast', a colloidal thorium oxide preparation ($^{232}$Th is an alpha emitter), as a contrast medium for diagnostic radiology. Bone cancers attributable to radium resulted from occupational exposure of radium dial painters to $^{226}$Ra and $^{228}$Ra and therapeutic treatments with $^{224}$Ra for medical conditions. There are extensive data on lung cancer resulting from occupational exposure of uranium miners to radon-222 and daughters, with consistent data from studies of residential exposure. In addition, an excess of leukaemia has been reported in Thorotrast-treated patients, and quantitative estimates of plutonium-239 induced lung cancer have been derived for Russian workers at the Mayak nuclear site (WHO 2001, Harrison and Muirhead 2003, Gilbert *et al* 2004, Sokolnikov *et al* 2008). Comparisons can be made between the risk estimates for radiation-induced cancer derived for these radionuclide exposures, and those derived for the A-bomb survivors (Harrison and Muirhead 2003). On the assumption that alpha particles are more effective than gamma rays per unit dose by a factor of 20, as assumed by ICRP, the incidence of liver cancer in Thorotrast patients is consistent with that in the A-bomb survivors. However, comparison of leukaemia incidence in the two population groups implies a relative biological effectiveness (RBE) for alpha particles of around 1 – 2. Animal data provide support for a low alpha RBE for leukaemia induction (Breckon and Cox 1990, Ellender *et al* 2001). Estimates of lung cancer risk in miners exposed to $^{222}$Rn and its short-lived alpha-emitting progeny, obtained using the ICRP respiratory tract model to calculate doses and an alpha particle RBE of 20, are within a factor of about 3 of estimates based of the A-bomb survivor data (Harrison and Muirhead 2003). Similar approximate risk estimates have been derived for $^{239}$Pu induced lung cancer in Mayak workers (Grogan *et al* 2001, Gilbert *et al* 2004), although there are large uncertainties

in estimates of lung dose. Recent combined case-control analyses have provided information on raised rates of lung cancer attributable to exposures to $^{222}$Rn and its progeny in homes (Darby *et al* 2005, 2006, Krewski *et al* 2006, Lubin *et al* 2004). Precise comparisons with risk estimates derived from the miner data and the A-bomb survivor data are difficult but they appear to be consistent (ICRP 2007).

While the available data provide support for the assumptions made regarding the equivalence of internal and external exposures, there are substantial uncertainties in the dose and risk estimates for internal emitters and the information relates to a few radionuclides. There is international recognition that all possible sources of additional quantitative information should be pursued.

### 2.2.3 Non-cancer risks from external and internal exposures

Raised risks from heart disease and stroke have been observed in a number of populations exposed to radiation. Mortality from stroke and heart disease in the A bomb survivors was analysed by Shimizu *et al* (2010) showing increased risks from both diseases associated with external radiation exposure, although for stroke the risks at low doses were small. For heart disease the study indicated a risk even at low doses but the evidence for this was extrapolated from doses above 0.5Gy and was not statistically significant at lower doses. Smoking and other lifestyle factors were taken into account but did not appear to affect the radiation risks. Heart disease risks have been extensively studied in medically exposed patients at high external doses, as reviewed by Darby *et al* (2010).

The Mayak worker cohort has shown statistically significant trends in ischemic heart disease and cerebrovascular disease incidence in relation to external dose and internal exposures from plutonium (Azizova *et al* 2010a,b). For external dose, there was a significant relationship between incidences (but not mortality) from these diseases, taking account of internal radiation exposures and relevant lifestyle factors. The results for internal exposure to plutonium were less clear but showed a significant correlation for cerebrovascular disease. The UK NRRW and the BNFL cohorts have been used to consider non-cancer diseases. Both cohorts showed excess risks for mortality from heart disease but the analyses were basic as neither took account of internal exposures or lifestyle factors (Muirhead et al 2009, McGeoghegan et al 2008). However, there is potential for more informative future analyses of these cohorts using additional data (eg. smoking histories) that have been recorded over the years which would greatly enhance their value.

A recent ICRP draft report (ICRP 2011a) on tissue injury concluded that for circulatory disease there is an approximate threshold dose of around 0.5 Gy, applying to acute and fractionated / protracted exposures. Review of evidence for radiation-induced cataract also suggested that any threshold for effects was lower than previously assumed and again it was concluded that the threshold should be taken to be around 0.5 Gy for both acute and fractionated exposures. The main sources of information on radiation-induced cataract are the A bomb survivor studies, follow-up of radiotherapy cases, post-Chernobyl studies, and studies of occupational exposures including those of astronauts and pilots. Taking account of the available data and conclusions in their report (ICRP 2011a), ICRP (2011b) has issued a statement on doses to the lens of the eye, recommending an annual occupational dose limit of 50 mSv, with no more than 100 mSv accumulated over 5 years.

A review on circulatory disease risk by the HPA Advisory Group on Ionising Radiation (AGIR 2010) reached similar conclusions to ICRP (2011a) but also suggested that the risk data are compatible with an LNT dose-response relationship as assumed for cancer. Similarly, an HPA review of cataract data (Ainsbury et al 2009) was consistent with the ICRP review but suggested that the effect might be stochastic and might best be described by an LNT model. However, for circulatory disease and cataract, current knowledge of mechanisms of radiation action is insufficient to make informed judgments on dose-response relationships. Raised

risks from heart disease and stroke have been observed in a number of populations exposed to radiation. Mortality from stroke and heart disease in the A bomb survivors was analysed by Shimizu *et al* (2010) showing increased risks from both diseases associated with external radiation exposure, although for stroke the risks at low doses were small. For heart disease the study indicated a risk even at low doses but the evidence for this was extrapolated from doses above 0.5Gy and was not statistically significant at lower doses. Smoking and other lifestyle factors were taken into account but did not appear to affect the radiation risks. Heart disease risks have been extensively studied in medically exposed patients at high external doses, as reviewed by Darby *et al* (2010).

The Mayak worker cohort has shown statistically significant trends in ischemic heart disease and cerebrovascular disease incidence in relation to external dose and internal exposures from plutonium (Azizova *et al* 2010a,b). For external dose, there was a significant relationship between incidences (but not mortality) from these diseases, taking account of internal radiation exposures and relevant lifestyle factors. The results for internal exposure to plutonium were less clear but showed a significant correlation for cerebrovascular disease. The UK NRRW and the BNFL cohorts have been used to consider non-cancer diseases. Both cohorts showed excess risks for mortality from heart disease but the analyses were basic as neither took account of internal exposures or lifestyle factors (Muirhead *et al* 2009, McGeoghegan *et al* 2008). However, there is potential for more informative future analyses of these cohorts using additional data (eg. smoking histories) that have been recorded over the years which would greatly enhance their value.

A recent ICRP draft report (ICRP 2011a) on tissue injury concluded that for circulatory disease there is an approximate threshold dose of around 0.5 Gy, applying to acute and fractionated / protracted exposures. Review of evidence for radiation-induced cataract also suggested that any threshold for effects was lower than previously assumed and again it was concluded that the threshold should be taken to be around 0.5 Gy for both acute and fractionated exposures. The main sources of information on radiation-induced cataract are the A bomb survivor studies, follow-up of radiotherapy cases, post-Chernobyl studies, and studies of occupational exposures including those of astronauts and pilots. Taking account of the available data and conclusions in their report (ICRP 2011a), ICRP (2011b) has issued a statement on doses to the lens of the eye, recommending an annual occupational dose limit of 50 mSv, with no more than 100 mSv accumulated over 5 years.

A review on circulatory disease risk by the HPA Advisory Group on Ionising Radiation (AGIR 2010) reached similar conclusions to ICRP (2011a) but also suggested that the risk data are compatible with an LNT dose-response relationship as assumed for cancer. Similarly, an HPA review of cataract data (Ainsbury *et al* 2009) was consistent with the ICRP review but suggested that the effect might be stochastic and might best be described by an LNT model. However, for circulatory disease and cataract, current knowledge of mechanisms of radiation action is insufficient to make informed judgments on dose-response relationships.

## 2.3 Internal emitters and ICRP

### 2.3.1 Biokinetic models

The first step in the calculation of doses from radionuclides taken into the body is the use of biokinetic models to represent the distribution and retention of elements and their radioisotopes in body organs and tissues. ICRP biokinetic models consider intakes by ingestion and inhalation by adults and children (ICRP, 1979, 1980, 1981, 1989, 1993, 1994a,b, 1995a,b,c). Doses to the fetus following maternal intakes have also been calculated (ICRP, 2001) and also doses to infants from radionuclides transferred to breast-milk (ICRP 2004). Models of the alimentary and respiratory tracts are used to define the movement of radionuclides within these systems, resulting in absorption to blood and/or loss from the body

(ICRP, 1979, 1994a, 2006). The behaviour of radionuclides absorbed to blood is described by element-specific systemic models (ICRP, 1979, 1980, 1981, 1989, 1993, 1995a,b,c). Systemic models range in complexity from very simple models that assume uniform whole-body distribution to multi-compartment recycling models that take account of movement within and between body organs and tissues. Thus, for example, the current models for tritium and isotopes of caesium consider uniform whole-body distribution with two components of retention while the models for strontium and plutonium are complex recycling models that represent uptake and retention in different skeletal tissues as well as other organs (ICRP, 1989, 1993).

The reliability of biokinetic models depends ultimately on the quality of the data on which they are based, including the availability of human data, but also on the realism of the model developed from these data. For a number of elements and their radioisotopes, there are few or no human data for use in model development or validation, and reliance is placed on the results of animal experiments and chemical analogues. There are continuing efforts to provide improved models and over the next few years the ICRP's intention will be to publish new and updated models, and dose coefficients calculated using these models, to follow the new recommendations (ICRP 2007).

Biokinetic models for individual elements and their radioisotopes are used to calculate the number of radioactive decays (transformations) occurring within specific tissues, organs or body regions (termed “Source” regions) during a given period of time. The integration period used by ICRP in the calculation of committed doses is to age 70y in all cases, applied to different ages of children and adults (age 20y). The extent of protraction of dose over the integration period will depend on the decay characteristics of the radionuclide and the duration of its retention in body tissues.

### 2.3.2 Dosimetric models

Dosimetric models are used to calculate the deposition of energy in all important organs/tissues (“Target” regions) for transformations occurring in each source region, taking account of the energies and yields of all emissions (Eckerman, 1994). Absorbed dose in gray (Gy) can then be calculated, knowing the number of decays occurring in source regions and energy deposition in target regions.

Dose calculations rely on the use of reliable information on half-life, modes of decay, and the energies and yields of the various radiations emitted by nuclides and their progeny (Eckerman et al, 1994, Endo et al, 2003). Because the radiation types differ in their ranges in tissues, it is particularly important to account for the fraction of the available decay energy dissipated by conversion electrons, Auger elections, and characteristic x-rays. Current calculations rely on nuclear decay data provided in Publication 38 (ICRP, 1983) but new calculations will use more extensive up-dated information made available as Publication 107 (ICRP, 2009).

Anthropomorphic phantoms are used to describe geometric relationship between different organs and tissues in the body. There are two main types of phantom – mathematical phantoms that approximate the sizes and shapes of organs mathematically (Cristy and Eckerman, 1987) and voxel phantoms that are based on imaging data for real individuals, obtained using computed tomography or magnetic resonance imaging (Zankl et al, 2002, 2003, 2007). ICRP has used mathematical phantoms (Eckerman, 1994; Stabin et al, 1999, ICRP, 2001) but these are being replaced by models based on voxelised images (Zankl et al, 2003, 2007, Fill et al, 2004). Reference adult male and female computational models have been completed (ICRP, 2009b), adjusting data from scanned images for consistency with ICRP reference data for body mass and related characteristics (ICRP 2002b). New reference computational phantoms will also be developed for children of different ages for use in the calculation of dose coefficients for members of the public (ICRP 2007). In addition to their

use for ICRP dosimetry, the new generation of phantoms are better suited for other applications. Thus, adjustments can be made to the body shape and organ dimensions of specific individuals so that they can be used, for example, for medical applications in which accurate estimates of absorbed doses are required.

Doses from “cross-fire” radiation between source and target regions (organs and tissues) are important for penetrating photon radiation. For “non-penetrating” alpha and beta particle radiations, energy will in most cases be largely deposited in the tissue in which the radionuclide is deposited. For all dose calculations, radionuclides are assumed to be uniformly distributed throughout source regions, but while these are generally whole organs (e.g. liver), they may be a thin layer within a tissue (e.g. bone surfaces). Similarly, target cells for induction of cancer and hereditary effects are assumed to be uniformly distributed throughout target regions but these vary in size from whole organs to layers of cells. As a consequence, source and target considerations are important for alpha and electron emissions in the specific cases of doses within the respiratory and alimentary tracts and the skeleton. Thus, doses are calculated to target layers within bronchial and intestinal epithelia from radionuclides in transit in the airways and gut lumen (ICRP, 1979, 1994a, 2006; Harrison et al, 2005, Phipps et al, 2007) and to the whole or peripheral red bone marrow from radionuclides on bone surfaces or in bone mineral (ICRP, 1979). Electron cross-fire is also taken into account in calculating doses to foetal tissues (ICRP, 2001). An important concern is whether these assumptions provide adequate assessments of dose and risk, particularly when considering the heterogeneous distribution of short-range charged particle emissions (e.g. alpha emitters, low energy beta emitters such as tritium, and Auger emitters) in relation to target cells and their nuclei.

### 2.3.3 Radiation weighting factors

The next stage in the ICRP methodology is the transition from absorbed dose, a scientific quantity given the special name, gray (Gy), to the ICRP protection quantity, equivalent dose, with the special name, sievert (Sv). The calculation of equivalent dose provides a method by which the individual radiation doses to a given tissue or organ, from various types of ionising radiation (alpha, beta, gamma and X-rays), can be summed in relation to the effect they produce and, specifically, in relation to cancer induction. To achieve this objective, major simplifications are made.

Different types of radiation are known to vary in their effectiveness in causing cancer (ICRP, 1991, 2003, 2007; UNSCEAR, 2000). Currently, a simple one-dimensional indicator of ionisation track structure, namely the linear energy transfer or LET, is generally used to inform judgements on biological effects (ICRP, 1991, 2003; UNSCEAR, 2000). Clustered DNA damage, together with the degree of complexity of the damage, has been shown to increase with LET (Nikjoo et al, 2002; ICRP, 2003). The two broad categories of radiation that require consideration in the context of internal dosimetry are photons and charged particles, the latter including electrons and alpha particles. Photons and electrons (beta particles) are low LET radiations, alpha particles have high LET. However, very low energy electrons (e.g. Auger electrons, beta emission from tritium, electrons released by absorption of low energy X-rays) have higher LET values than higher-energy beta-particle emissions or electrons generated by conversion of gamma photons.

In practice, the assessment of the different effectiveness of different radiations relies on data on their Relative Biological Effectiveness (RBE), defined as the ratio of the absorbed dose of a reference radiation to the absorbed dose of a test radiation required to produce the same level of effect. RBE is therefore an empirical quantity, which depends on the biological system, the observed end-point and the conditions of the experiment. Values are usually found to vary with dose and dose rate, increasing for high LET radiation to a maximum value at low dose and dose rate because of a curvilinear response at higher acute doses of the

reference low LET radiation. $RBE_{MAX}$ values are applicable to estimation of stochastic risk at low doses (ICRP, 2003).

Radiation weighting factors ($w_R$) are chosen by ICRP as a simplified representation of the different effectiveness of radiations per unit absorbed dose in causing cancer. These simplifications are considered appropriate for the specified purposes of the protection quantities. Thus, despite differences in RBE between different low LET radiations and observations of different alpha particle RBE values for different end-points (UNSCEAR, 2000; ICRP, 2003; Harrison and Muirhead, 2003), ICRP calculate equivalent dose using radiation weighting factors of 1 for all low LET radiations and 20 for alpha particles.

The equivalent dose, $H_{T,R}$, in tissue or organ $T$ due to radiation $R$, is given by:

$$H_{T,R} = w_R D_{T,R}$$

The total equivalent dose to an organ or tissue, $H_T$, is the sum of $H_{T,R}$ over all radiation types:

$$H_T = \sum_R H_{T,R}$$

### 2.3.4 Tissue weighting factors

The purpose of the final stage in the ICRP methodology is to relate dose to risk in a simple manner, summing all radiation doses to all tissues in one risk-related protection quantity, the effective dose (Sv). To combine equivalent doses to different organs and tissues, tissue weighting factors ($w_T$) are used to express the contribution of individual organs and tissues to overall detriment from cancer and hereditary effects, relating to whole body radiation exposure.

The effective dose, E, is given by:

$$E = \sum_T w_T H_T$$

Table 1 compares the $w_T$ values used currently (ICRP, 1991) and the values introduced in the new ICRP recommendations (ICRP, 2007). As discussed in section 2.1, the main source of data on cancer risks is the follow-up studies of the Japanese atomic bomb survivors. As well as longer follow-up, the new $w_T$ values are based on cancer incidence rather than fatality data, adjusted for lethality and loss of quality of life. Weighting for hereditary effects is now based on estimates of disease in the first two generations rather than at theoretical equilibrium. The main changes in $w_T$ values in the new recommendations are an increase for breast (from 0.05 to 0.12), a decrease for gonads (from 0.2 to 0.08) and inclusion of more organs and tissues in a larger “Remainder” (from 0.05 to 0.12).

**Table 1. ICRP tissue weighting factors ($w_T$)**

| Organ / tissue | ICRP (1991) | ICRP (2007) |
|---|---|---|
| Breast | 0.05 | 0.12 |
| Bone marrow | 0.12 | 0.12 |
| Colon | 0.12 | 0.12 |
| Lung | 0.12 | 0.12 |
| Remainder | 0.05 | 0.12[a] |
| Stomach | 0.12 | 0.12 |
| Gonads | 0.20 | 0.08 |
| Bladder | 0.05 | 0.04 |
| Liver | 0.05 | 0.04 |
| Oesophagus | 0.05 | 0.04 |
| Thyroid | 0.05 | 0.04[c] |
| Bone surfaces | 0.01 | 0.01 |
| Brain[d] | - | 0.01 |
| Salivary glands[d] | - | 0.01 |
| Skin | 0.01 | 0.01 |

[a]*The ICRP (2007) weighting factor of 0.12 for Remainder is apportioned equally between 13 organs/tissues in males and females: Adrenals, Extrathoracic tissue, Gall bladder, Heart, Kidneys, Lymphatic nodes, Muscle, Oral mucosa, Pancreas, Prostate (♂), Small intestine, Spleen, Thymus, Uterus/cervix (♀).*
[b]*Combined detriment from ovarian cancer and hereditary effects.*
[c]*The weighting factor for the thyroid was set at 0.04 to take account of evidence of a pronounced elevation of risk in childhood.*
[d]*Salivary glands and brain were given weighting factors of 0.01 because cancer risks, while not separately quantifiable, were judged to be greater than for other tissue in the Remainder.*

Tissue weighting factors are based on values of relative detriment, calculated separately for males and females and applying to populations of all ages. These relative detriment values and corresponding absolute detriment values are given in Annex A of the new recommendations (ICRP, 2007). The overall detriment value for females is 40% greater than for males. The largest differences for individual organs are factors of 0.4, 0.5, 2.0 and 4.2 for females compared to males, for colon, liver, lung and thyroid, respectively. In addition, breast cancer accounts for about one-quarter of the total detriment in females. The male and female detriment and cancer incidence data tabulated by ICRP (2007) apply to populations of all ages. The BEIR VII report (NAS/NRC, 2006) provides estimates of life-time attributable risk for radiation exposure of males and females at different ages. These data show that risk estimates are generally about double for irradiation in infancy compared with age 20y, and about 5 – 6 times greater for thyroid cancer.

### 2.3.5 Use of equivalent and effective dose

The ICRP publishes dose coefficients (Sv $Bq^{-1}$) for intakes of individual radionuclides, giving values of committed equivalent dose to individual organs and tissues, and committed effective dose (ICRP 1996, 2001). ICRP dose coefficients are calculated using defined biokinetic and dosimetric models, including reference anatomical data for the organs and tissues of the human body. They are calculated for reference adults, children of different ages and the fetus at different stages of development. They do not take account of individual characteristics. Radiation weighting factors are chosen as a simple representation of the

different effectiveness of different radiations in causing stochastic effects at low doses and dose rates. They do not take account, for example, of observed differences between low LET radiations (eg. photons of different energies), and of different alpha particle RBE values for different cancer types. A single set of tissue weighting factors is used to take account of the contribution of individual organs and tissues to overall detriment from cancer and hereditary effects, despite age and gender related differences. Doses to male and female adults will in future be calculated separately using new anatomical models but equivalent doses to males and females will be averaged before calculation of effective dose.

As discussed by Harrison and Day (2008), there is an apparent inconsistency between the increasing realism and complexity of biokinetic and dosimetric models and the continued use of a simple sets of radiation and tissue weighting factors. However, while the biokinetic and dosimetric models are primarily intended for use in the calculation of ICRP dose coefficients, they can be more widely applied. For example, they can be and are used to calculate absorbed doses to specific organs and tissues, both in the assessment of risks of stochastic effects and in the assessment of deterministic effects at higher doses. The models can also be used to provide dose estimates for epidemiological studies and in probability of causation calculations. The new generation of adjustable computational phantoms is ideally suited for these other applications. In contrast, radiation and tissue weighting factors are to be used solely in the calculation of the ICRP protection quantities, to provide a method for comparing all radiation exposures with dose limits and constraints. It would not be practicable to devise an internationally applicable system that would take account of recognised age-, sex- and population- related differences in risk factors and differences between radiation types. Increased complexity would create a false impression of the certainty with which radiation risks at low doses are understood. Central to the ICRP system is the optimisation of protection below constraints (ICRP, 2007); constrained optimisation should ensure appropriate levels of protection, using the protection quantities with their inherent simplifications.

## 2.4 New ICRP dose coefficients

The 2007 ICRP Recommendations introduced revised weighting factors, as discussed above (Section 3.4), that require the recalculation of all dose coefficients for external and internal exposures of workers and members of the public. In Publication 103 (ICRP 2007), for the first time ICRP has also adopted reference anatomical models for use in dose calculations, based on medical imaging data (Section 3.2). Reference adult male and female computational phantoms have been published (ICRP 2010) and will be used to calculate equivalent doses separately for males and females, averaging these equivalent dose values in the calculation of effective dose (ICRP 2007).

For the recalculation of dose coefficients, the opportunity is being taken to improve biokinetic as well as dosimetric models. Intakes of radionuclides by inhalation will continue to be modelled using the Human Respiratory Tract Model, HRTM (ICRP 1994a) but a number of changes are being introduced to take account of more recent information on particle clearance in the alveolar and bronchial regions of the lungs and the extrathoracic region of the respiratory tract (Bailey et al 2007, 2008). For ingested radionuclides, the Human Alimentary Tract Model, HATM (ICRP 2006) will be used instead of the Publication 30 (ICRP 1979) gastrointestinal model, the most important change being the explicit calculation of doses to target regions in gut epithelium. Element-specific systemic models of the organ and tissue retention and excretion of radionuclides absorbed to blood are being updated as appropriate, with all new models having increased physiological realism, including the explicit modelling of urinary and faecal excretion.

The first update to be published will be the revision of Publication 74 (ICRP 1996) giving dose conversion coefficients for external radiation exposures, calculated using updated nuclear decay data (ICRP 2009a) and the new reference adult phantoms (ICRP 2009b). Use of the new voxel phantoms to calculate organ and tissue doses will be complemented by improved treatment of skeletal dosimetry. In this methodology, combinations of microCT images (displaying the 3D structure of the marrow cavities and bone trabeculae) are coupled with computation models of the individual bones of the skeleton (displaying the 3D structure of cortical bone, trabecular spongiosa, and medullary marrow of the long bones) to properly account for radiation transport estimates of absorbed fractions for different source regions and skeletal target regions (Hough et al 2011, Johnson *et al* 2011). The next priority will be a series of reports on occupational intakes of radionuclides, replacing the Publication 30 series (ICRP 1979, 1980, 1981, 1988) and Publication 68 (ICRP 1994b) to provide revised dose coefficients for radionuclide inhalation and ingestion. The reports in this series will provide data for the interpretation of bioassay measurements as well as giving dose coefficients, replacing Publications 54 and 78 (ICRP 1989, 1997).

For the calculation of new dose coefficients for the ingestion and inhalation of radionuclides by members of the public, a series of reference paediatric phantoms is being developed. A paediatric phantom report will be published to include anatomical models of the Publication 89 (ICRP 2002b) reference newborn, 1-year, 5-year, 10-year, and 15-year children. These phantoms are being developed at the University of Florida, first in a “hybrid” format consisting of combinations of polygon mesh and non-linear rational B-spline surfaces, and later voxelized for radiation transport calculations (Lee *et al* 2010). Skeletal samples have been collected for microCT image acquisition and analysis, for radiation transport in different skeletal source tissues. Using these phantoms, and updated systemic biokinetic models, reports will be produced to replace Publications 56, 67, 69 and 72 (ICRP 1990, 1992, 1995(a), 1995(c)), giving dose coefficients for the ingestion and inhalation of a range of radionuclides by members of public, including children. Work is also in progress on foetal models for eight stages: 8, 10, 15, 20, 25, 30 and 38 weeks of gestation. These will be used to provide revised dose coefficients for radiation exposures of newborn children, following radionuclide intakes by their mothers and transfer to the fetus during pregnancy and suckling infant in breast-milk, replacing Publications 88 and 95 (ICRP 2001, 2004).

## 2.5 Research on doses and risks from internal emitters

It is generally the case that doses and risks from internal emitters are more difficult to evaluate and more uncertain than doses and risks from external radiation. The adequacy of protection for internal emitters has been questioned (eg. CERRIE 2004) and assumptions made in modelling doses and controlling risks continue to be the subject of concern and some controversy. For example, Raabe (2010) interpreted human and animal data on bone and lung cancer caused by internal emitters as showing that the effects of chronic life-span irradiation is dose-rate dependent, with the time taken to develop cancer increasing at lower dose rates such that a practical threshold results when the natural life-span is exceeded. Raabe (2010) and others have concluded that cumulative radiation dose is neither an accurate nor an appropriate measure of cancer risk associated with protracted ionizing radiation exposure.

An important research priority is to make best use of opportunities for epidemiological studies on the effects of internal emitters, concentrating on those situations where doses have been recorded or can be reconstructed. The nuclear industry and particularly reprocessing and weapons manufacture have resulted in worker exposures to a number of radionuclides, including isotopes of plutonium and uranium, and also tritium (UNSCEAR 2000). Liquid and

gaseous releases, including those occurring during accidents have led to exposures to a range of radionuclides, including isotopes of strontium and iodine (UNSCEAR 2000). Because the largest exposures occurred mostly in the late 1940s and early 1950s, effort is required now to ensure that the maximum amount of quantitative information can be obtained from such studies.

While epidemiological studies may provide insights into radiation action, they cannot provide definite answers to questions concerning the mechanisms of disease induction and progression. In principal, there is no fundamental difference between external radiation and internal emitters in that they both cause damage to molecular structure within cells as a result of ionisations. However, there are specific issues relating only to internal emitters that require separate consideration, arising because of the short range of some radioactive emissions and the density of ionisation (CERRIE 2004, Harrison and Day 2008). Thus, for alpha particles and low energy electrons, it is important to understand (i) how effects are modulated by the location of the radionuclide relative to cells which sustain damage that may lead to disease, and (ii) the relationship between spatial and temporal density of ionisation and the effects caused. (UNSCEAR 2000, 2006a,b, EC 2009, www.melodi-online.eu). The following sections consider the examples of research into health effects of inhaled plutonium-239 in adults and *in utero* exposures to strontium-90 and other radionuclides, concentrating on epidemiological studies and associated dosimetric modelling.

### 2.5.1 Inhalation of plutonium-239 and other radionuclides by workers

Analyses of cancer risk associated with plutonium exposures in the Russian Mayak worker cohort, referred to above (Section 2.2), have shown statistically significant increases in lung and liver cancers for both males and females (with risks higher for females) (Sokolnikov *et al* 2008). A similar trend was found for bone cancers in this cohort but this association was driven by excess cancers at very high doses (>10Gy). External doses and some lifestyle factors were accounted for in these analyses. The Mayak worker cohort includes about 7,800 plutonium workers.

The observations in the Mayak worker cohort of plutonium related lung, liver and bone cancer is consistent with expectations in terms of sites of retention and modelled doses. However, an interesting observation is the lack of leukaemia induction associated with plutonium exposure. Shilnikova *et al* (2003) demonstrated a significant doe-response relationship between external dose and leukaemia but with no indication of an effect of plutonium exposure. Thus it appears that skeletal deposits of $^{239}$Pu, and the resulting alpha particle irradiation, result in bone cancer but are ineffective in causing leukaemia.

The UK BNFL worker cohort includes 12,272 plutonium workers with extensive measurements of plutonium in urine samples. In general, cumulative plutonium exposures are lower in the BNFL worker cohort than in the Mayak worker cohort. The two cohorts are complementary and it is considered appropriate to undertake a joint analysis as well as separate analyses of plutonium related disease. Analyses of the Mayak and BNFL worker cohorts forms part of the work programme of the EC FP7 Framework project, SOLO. In addition, there are plutonium workers in other UK cohorts (UKAEA and AWE) that should be included in future analyses. Furthermore, there is the potential to compare the Russian and UK plutonium worker cohorts with similar cohorts from other countries, in particular those from France and the USA.

An important aspect of the assessment of risks of plutonium exposure is the estimation of organ/tissue doses. Reconstructing plutonium doses from bioassay measurements and work histories is highly complex and subject to considerable uncertainties. Within European and US funded studies, substantial progress has been made in reaching a consensus with Russian colleagues on the best approaches to assigning individual doses and also to

calculate uncertainties associated with dose estimates (Birchall *et al* 2010, Puncher *et al* 2011). ICRP models are being used for these calculations to assess the pattern of intake, principally by inhalation, in relation to measurements of urinary excretion. In limited cases, autopsy measurements of organ retention of plutonium are also available and can be used to improve dose assessments and validate or improve model assumptions. A particular difficulty is taking account of the different solubilities of the various chemical forms of plutonium that may have been inhaled in different working environments. These differences in solubility can be large – between oxides and nitrates, for example – and effect the relationship between retention of plutonium in the lung, its subsequent retention in other body organs, mainly liver and skeleton, and its excretion in urine and faeces. It is essential that consistent approaches to dosimetry are applied in separate and joint analyses of the Mayak, UK BNFL Sellafield, and other cohorts.

A significant challenge to current protection standards is whether circulatory disease should be included with cancer and hereditary effects in low dose detriment estimates. As discussed above (Section 2.3), studies are in progress into non-cancer as well as cancer incidence in the Mayak cohort in relation to internal plutonium exposures as well as external radiation and similar studies have been initiated for the BNFL Sellafield cohort. Parallel and joint analyses will maximise the information obtained from future studies of these and other cohorts. Worker cohorts are ideally suited to studies of cancer and non-cancer disease at protracted low dose and dose rate exposures to external sources and internal emitters, with the potential to use additional lifestyle information (eg. smoking histories) to enhance the analyses.

In addition to studies of plutonium exposures, worker cohorts can be used to quantify the effects of other radionuclides, including isotopes of uranium. The biokinetics and dosimetry of alpha emitting isotopes of uranium suggest that the main effects observable following sufficiently high exposures will be lung and bone cancer, with the possibility of kidney cancer (ICRP 1995a,b,c). A recent French study suggested a link between lung cancer risk and exposure to reprocessed uranium oxide (Canu et al 2010). In the UK BNFL cohort, exposure to uranium will have occurred at Springfields and also at Sellafield and Capenhurst. Exposure to uranium will also have been experienced by a number of UKAEA and AWE workers. It would be appropriate to analyse a combined UK worker cohort separately and also consider joint analyses with French data. Exposure to uranium will also have occurred in the USA and Russia. The interest in uranium exposures extends to the military use of depleted uranium as well as uranium use in the nuclear industry.

Tritium exposures of workers occur predominantly as tritiated water and the resulting dose, although delivered by short range beta particles is essentially distributed throughout the body (HPA 2007). The distribution of cancer types resulting from sufficiently high intakes would therefore be expected to be indistinguishable from that observed following exposures to uniform whole-body external radiation. However, considerable attention has been focused on the possible health effects of tritium and the RBE of beta particle emissions from tritium compared to gamma rays (HPA 2007, Cox et al 2008). The issue is of particular importance in Canada because of the higher levels of tritium exposure that occur during the operation of their CANDU reactors. However, there were also UK tritium workers at BNFL (Sellafield, Capenhurst and Chapelcross), UKAEA (Winfrith, Harwell and Dounreay), the AWE sites (Aldermaston) and the former Amersham International. The best approach to an epidemiological study of tritium exposed workers would be an international pooling to include Canadian, UK, French, US and Russian workers who have been exposed to tritium under a variety of circumstances. The use of tritium in kilogram quantities in future commercial nuclear fusion power stations, with the present construction of the ITER (International Thermonuclear Experimental Reactor) in France, provides an additional reason to study the health effects of tritium.

### 2.5.2 *In utero* exposures from $^{90}$Sr and other radionuclides from the Techa River

In the late 1940s and 1950s, many thousands of people living in rural villages on the Techa River received protracted external and internal radiation exposures as a result of discharges of radionuclides from the Mayak plutonium production complex, particularly during the early years of its operation (Krestinina *et al* 2005, Degteva *et al* 2007). The dominant source of dose to red bone marrow and hence the major determinant of the risk of leukaemia, was intakes by ingestion of beta particle emitting isotopes of strontium, principally strontium-90 (Degteva *et al* 2007). Strontium-90 and its immediate decay product, yttrium-90, emit beta particles with mean energies of about 0.2 MeV and 1 MeV, respectively, and ranges in soft tissue of up to 2 mm and 10 mm, respectively. Krestinina *et al* (2005) reported a preliminary analysis of cancer mortality in a cohort of almost 30,000 people born before 1950 who lived near the river sometime between 1950 and 1960. Further work is required to provide improved estimates of doses received by cohort members using a Techa-specific modification of the ICRP alkaline earth model (Shagina *et al* 2003). However, based on 1842 solid cancer deaths and 61 deaths from leukaemia, it was estimated that 2.5% of solid cancers and 63% of leukaemia deaths were attributable to radiation (Krestinina *et al* 2005). Because, dose to red bone marrow was dominated by strontium-90, this study provides direct evidence of the induction of leukaemia by beta particles from strontium-90 and yttrium-90.

Work is in progress to assess *in utero* and postnatal doses to a Techa River Offspring Cohort, including haemopoietic tissue doses delivered primarily by strontium-90 (Shagina *et al* 2007). This has involved adaptation of the ICRP (1993) alkaline earth model as applied to the mother and the ICRP (2001) alkaline earth model for the fetus. The foetal model was developed by Fell *et al* (2001), using data for the calcium content of the developing foetal skeleton to determine rates of transfer from maternal to foetal blood. Account was taken of maternal changes in calcium metabolism during pregnancy, including increases in intestinal absorption, bone turnover and urinary excretion. The models were then applied to strontium and other alkaline earth elements, with transfer from maternal blood to foetal blood reduced compared to that for calcium on the basis of information on placental discrimination. Shagina *et al* (2003, 2007) adapted both the adult and foetal models, taking account of Russian data and particularly Techa-specific data. This included Russian data on the Ca content of the fetus in late gestation and on changing placental discrimination against strontium relative to calcium. Results for the transfer of strontium to the fetus were validated against Russian data for the uptake of stable strontium by the foetal skeleton and by data obtained for Techa River residents on strontium-90 in mothers and stillborn foetuses (Borisov 1973, Tolstykh *et al* 2001). Figure 1 shows the very good agreement obtained between modelled and measured values of transfer of stable strontium (Shagina *et al* 2007).

A complication in the assessment of *in utero* dose of relevance to the induction of leukaemia is the multiple and changing sites of haemopoiesis during embryonic and foetal development. The red bone marrow is the recognised target for leukaemia induction in children and adults, or more precisely, haemopoietic stem cells within bone marrow. In the embryo and fetus, however, although the bone marrow becomes established as the main site of haemopoiesis in the last few months of foetal life, the liver is an active site of haemopoiesis in mid-gestation and the stem cells that seed the liver and bone marrow may originate in the yolk sac or in an intra-embryonic site, the aorta-gonad-mesonephros (AGM) region (Metcalf and Moore 1971, Medvinsky *et al* 1993, Campagnoli *et al* 2000). While it is important to recognise the uncertainties introduced by this complex pattern of development, the concentration of strontium in bone mineral will result in much greater doses to foetal skeletal tissues than to soft tissues of the embryo and fetus. There is evidence that marrow haemopoiesis complements liver haemopoiesis from the beginning of the 2$^{nd}$ trimester (Wilpshaar *et al* 2002, Lim *et al* 2005, Tavian and Peault 2005a,b) and the approach being adopted on the

basis of current knowledge is to calculate marrow doses from 12 weeks of gestation onwards (Shagina *et al* 2007).

Improved phantoms are being developed for this work at the University of Florida, with detailed consideration of skeletal structures based on computed tomographic (CT) images (Jokisch *et al* 2001, Shah *et al* 2005a,b, Bolch *et al* 2007). CT images are used as the basis for Paired-Image Radiation Transport (PIRT) models that simultaneously track electrons at the macroscopic level of the entire skeleton and the microscopic detail of bone structure and sites of active marrow. These models take account of electron escape from bone regions and electron cross-fire between tissues. The foetal phantoms developed for this work will provide the basis for ICRP reference phantoms (see Section 4).

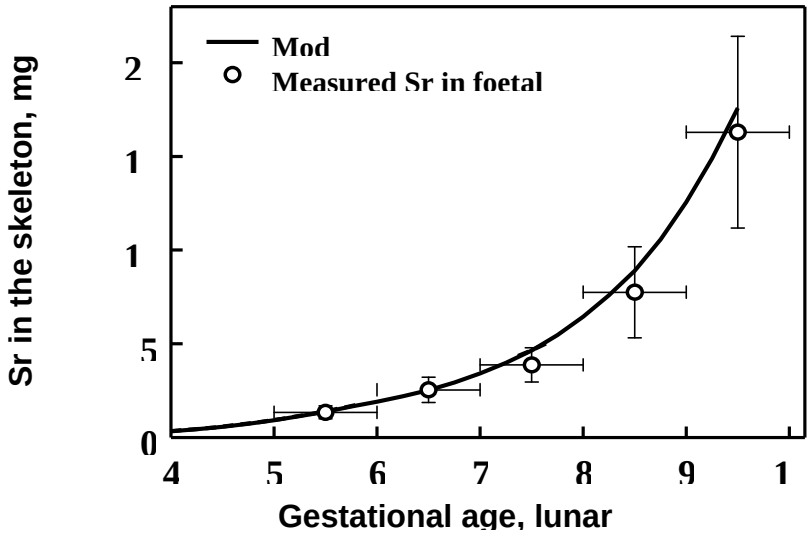



**Figure 1. Results of modelled transfer of stable strontium to the foetal skeleton from maternal diet compared with the measurement data of Borisov (1973).**

## 2.6 Uncertainties in dose and risk estimates

Because ICRP dose coefficients are calculated as reference values, applying to reference persons, they are not regarded as subject to uncertainty (ICRP 2007, Harrison and Day 2008). Thus, in general, point estimates of effective dose are used with no consideration of uncertainties. An exception may be occupational exposures in which uncertainties are assessed for the exposure conditions. In such a case, a range on intake would result in a range on effective dose, calculated using reference dose coefficients. Similarly, uncertainties in effective doses to members of the public might be related to a probability distribution on concentrations of a radionuclide in a food material.

It is recognised, however, that there are uncertainties associated with all aspects of the estimation of doses and risks at low doses. Uncertainties in biokinetic models and their parameter values depend on the availability of reliable data and often include the applicability of animal data to humans. Dosimetric uncertainties include the treatment of source and target distributions within tissues for radionuclides with short-range emissions. RBE values are often difficult to assess from available animal and human data and the applicability of *in vitro* end-points to cancer in humans may be questionable. Uncertainties in estimates of cancer risks include assumptions regarding the transfer of risks across populations, the validity of different risk models, the use of a dose and dose- rate effectiveness factor (DDREF) and the use of a linear dose-response relationship at low doses (ICRP 2007,

Harrison and Day 2008). While it is possible, in principle, to estimate uncertainties in tissue doses, RBE and risk estimates, these cannot be translated simply into uncertainties in effective dose. Since equivalent and effective doses are not calculated as best estimates for specific individuals or groups, they are not amenable to direct quantification of uncertainties. The control of exposures relies on the principles of optimisation of protection, using constraints and reference levels (ICRP 2007). However, an understanding of the component uncertainties in the calculation of dose coefficients can be seen as important, if challenging (ICRP 2007, Harrison and Streffer 2007, Harrison and Day 2008). It is clear that consideration of uncertainties is appropriate when considering estimates of organ doses in epidemiological studies or calculations of probability of cancer causation.

In the majority of published epidemiological studies, uncertainties in dose estimates are not taken into account. For example, risks from inhaled plutonium-239, discussed above (Section 5.1) have been derived using point estimates of lung dose that are calculated on the basis of urine or faecal bioassay measurements (Gilbert *et al* 2004, Sokolnikov *et al* 2008). Such estimates, however, ignore errors in lung dosimetry. As a consequence, there has been significant interest in applying Bayesian inference methods to calculate uncertainties on these estimates. Miller (2008) derived prior distributions of biokinetic model parameters with a view to applying them in a Bayesian analysis of doses to Mayak workers. This distribution was limited to a small set of biokinetic “types”, each type consisting of a vector of parameter values associated with a biokinetic model, derived by fitting the data to one of 41 sets of worker bioassay and autopsy data. However, representing the prior uncertainty on parameters as a discrete set of vectors rather than as continuous distributions may distort the uncertainty on dose and may also make it difficult to distinguish shared from unshared parameters. Puncher *et al* (2011) derived uncertainties in the ICRP Human Respiratory Tract Model, in the form of a multivariate continuous prior distribution. This was used to calculate uncertainties on lung doses for 2056 European nuclear workers in an on-going European case-control study of lung cancer risk from occupational exposures to actinides (Tirmarche *et al* 2010). Although the Bayesian calculation was performed separately for each worker, the sampling regime was implemented so that parameters identified as being shared or unshared would be preserved between workers.

## 2.7 Conclusions

This paper has explored the relationship between the scientific estimation of doses and risks from internal emitters and the use by ICRP of reference dose coefficients to control exposures to internal emitters. For the purposes of the protection system, ICRP assume that cancer risk estimates for external radiation exposures apply also to internal emitters when allowance is made for radiation quality, the relative effectiveness of different types of radiation in causing cancer. Biokinetic and dosimetric models are used to calculate doses from individual radionuclides, a simple adjustment is made for radiation quality in the majority of cases, and doses are then summed with and treated in the same way as those from external radiation in the calculation of effective dose for comparison with dose limits, constraints and reference levels. However, the adequacy of this procedure in providing protection from internal emitters continues to be questioned on the grounds that the spatial and temporal dose distribution within tissue and even cells can be very different between different internal emitters and from external radiation and this may affect the risks.

In a limited number of cases, risks from internal emitters can be quantified directly in epidemiological studies. The information from these studies provides support for the assumption of equivalence between risks from internal emitters and external radiation (Harrison and Muirhead 2003, UNSCEAR 2006). This equivalence is also supported in general by animal data and mechanistic studies. However, such comparisons may conceal

some of the complexity of dose – response relationships as a function of dose rate. For example, Raabe (2010) has analysed animal and human data on cancer caused by internal emitters and concluded that effects are dose rate dependent with a low dose rate threshold. These analyses suggest that, at least for particular cancer types, cumulative radiation exposure may overestimate risks at low doses and low dose rates. Further research is required to improve our understanding of dose – response relationships for different cancers and other diseases.

The highest priority for research on internal emitters must be to gain the maximum possible information from the limited opportunities for epidemiological studies. Worker cohorts are ideally suited to studies of cancer and non-cancer disease at protracted low dose and dose rate exposures to external sources and internal emitters, with the potential to use additional lifestyle information (eg. smoking histories) to enhance the analyses. Such studies will provide information of direct relevance to the protection system, including the use of a DDREF of two for solid cancers, reliance on the assumption of an LNT dose-response relationship at low doses, as well as the summation of doses from external radiation and internal emitters. They will also help determine whether low dose detriment should include non-cancer risks such as circulatory disease. In addition to worker cohorts, the Russian Techa River cohorts exposed to radionuclide discharges from the Mayak plutonium plant provide a unique opportunity to study effects of external radiation in comparison with internal emitters, principally strontium-90, at different ages including *in utero* exposures.

Epidemiological studies require best estimates of organ and tissues doses, preferably with associated uncertainties. Although the biokinetic and dosimetric models published by ICRP were developed primarily for the calculation of the protection quantities, equivalent and effective dose, they are also the best available models for adaptation for the calculation of doses to individuals for risk assessment purposes. Following the publication of new recommendations in 2007, ICRP has a substantial programme of research and development of models which are more physiologically realistic so that they are better able to reconstruct doses from bioassay data and properly represent anatomical structures as visualised by medical imaging procedures.

Models are being developed for children as well as adults and also for the pregnant woman and fetus. These models make best use of available scientific information and they should be seen as research tools as well as providing the basis for calculations underpinning protection standards.

While epidemiological studies may provide insights into radiation action, they cannot provide definite answers to questions concerning the mechanisms of disease induction and progression. In principal, there is no fundamental difference between external radiation and internal emitters in that they both cause damage to molecular structure within cells as a result of ionisations. However, there are specific issues relating only to internal emitters that require separate consideration, arising because of the short range of some radioactive emissions and the density of ionisation. Thus, for alpha particles and low energy electrons, it is important to understand (i) how effects are modulated by the location of the radionuclide relative to cells which sustain damage that may lead to disease, and (ii) the relationship between spatial and temporal density of ionisation and the effects caused.

It is important that the scientific basis for protection standards continues to be questioned and improved. Current assumptions made by ICRP in its recommended protection system make appropriate use of the available scientific evidence. Effective dose is an elegant protection tool that allows exposures to external radiation and internal emitters to be controlled using a single quantity. However, considerable uncertainties remain regarding risks at low doses and dose rates. Further research is required, prioritising epidemiological studies with supporting dosimetric modelling, but with parallel mechanistic studies. In

Europe, an important initiative is the setting up of the Multidisciplinary European Low Dose Risk Research Initiative (MELODI) to establish a research platform of European laboratories to coordinate work on low-dose radiation risks (www.melodi-online.eu), initially supported by an EU FP7 Framework Programme project (www.doremi-noe.net).

## 2.8 References

AGIR (2010). Circulatory Disease Risk. Advisory Group on Ionising Radiation Subgroup on Circulatory Disease Risk. RCE 16, HPA Chilton.

Ainsbury EA, Bouffler SD, Dörr W, Graw J, Muirhead CR, Edwards AA and Cooper J (2009). Radiation Cataractogenesis: A Review of Recent Studies. Radiat Res 172, 1-9.

Allison W (2009). Radiation and reason. The impact of science on a culture of fear. ISBN 0-9562756-1-3, York Publishing Services, York.

Azizova TV, Muirhead CR, Druzhinina MB, Grigoryeva ES, Vlasenko EV, Sumina MV, O'Hagan JA, Zhang W, Haylock RGE and Hunter N (2010a). Cardiovascular Diseases in the Cohort of Workers First Employed at Mayak PA in 1948-1958. Radiat Res 174, 155-168.

Azizova TV, Muirhead CR, Druzhinina MB, Grigoryeva ES, Vlasenko EV, Sumina MV, O'Hagan JA, Zhang W, Haylock RGE and Hunter N (2010b). Cerebrovascular Diseases in the Cohort of Workers First Employed at Mayak PA in 1948-1958. Radiat Res 174, 851-864.

Bailey MR, Ansoborlo E, Guilmette RA and Paquet, F (2007). Updating the ICRP Human Respiratory Tract Model. Radiat. Prot. Dosim., 127, 31-4.

Bailey MR, Asoborlo E, Etherington G, Gregoratto D, Guilmette R, Marsh J, Paquet F and Smith J (2008). Proposed updating of the ICRP Human Respiratory Tract Model. IRPA 12: Proc. 12th Int. Congr. Of the Int. Radiation Protection Association.

Birchall A, Puncher M, Harrison JD, Riddell A, Bailey MR, Khokryakov VF and Romanov SA (2010). Plutonium worker dosimetry. Radiat Environ Biophys 49, 203-12.

Bolch WE, Shah AP, Watchman CJ, Jokisch DW, Patton PW, Rajon DA, Zankl M, Petoussi-Henss N and Eckerman KF (2007). Skeletal absorbed fractions for electrons in the adult male: consideration of a revised 50 µm definition of the bone endosteum. Radiat Prot Dosim 127, 169-73.

Borisov BK (1973). Weight Indexes of Human Fetus Development and Strontium and Calcium Abundance in the Skeleton. (Moscow: Atomizdat) (in Russian).

Breckon G and Cox R (1990). Alpha particle leukaemogenesis. Lancet 1, 656-7.

Campagnoli C, Fisk N, Overton T, Bennett P, Watts T and Roberts I (2000). Circulating hematopoietic progenitor cells in first trimester fetal blood. Blood 95, 1967-72.

Canu IG, Jacob S, Cardis E, Wild P, Caer-Lorho S, Auriol B, Laurier D and Tirmarche M (2010). Reprocessed uranium exposure and lung cancer risk. Health Phys 99, 308-13.

CERRIE (2004). Report of the Committee Examining Radiation Risks of Internal Emitters. ISBN 0-85951-545-1.

Cox R, Menzel H and Preston J (2008). Internal dosimetry and tritium – the ICRP position. J Radiol Prot 28, 131-35.

Cristy M and Eckerman KF (1987). Specific absorbed fractions of energy at various ages from internal photon sources. ORNL/TM-8381/VI-7 (Oak Ridge, TN: Oak Ridge National Laboratory).

Darby S, et al (2005). Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. Br J Med 330, 223 6.

Darby S, et al (2006). Residential radon and lung cancer – detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14208 persons without lung cancer from 13 epidemiologic studies in Europe. Scand. J. Work Environ. Health 32 (Suppl. 1), 1-84.

Darby SC, Cutter DJ, Boerma M, et al (2010). Radiation related heart disease: Current knowledge and future prospects. Int J Radiation Oncology Biol Phys 76, No.3, 656-665.

Degteva MO, Shagina NB, Tolstykh EI, Bougrov NG, Zalyapin VI, Anspaugh LR and Napier BA (2007). An approach to reduction of uncertainties in internal dose reconstructed for the Techa River population. Radiat Prot Dosim 127, 480-5.

Eckerman KF (1994). Dosimetric methodology of the ICRP Internal Radiation Dosimetry ed O.G. Raabe (Wisconsin: Medical Physics Publishing), pp239 70.

Eckerman KF, Westfall RJ, Ryman JC and Cristy M (1994). Availability of nuclear decay data in electronic form, including beta spectra not previously published. Health Physics 67, 338-45.

Ellender M, Harrison JD, Pottinger H and Thomas JM (2001). Induction of osteosarcoma and acute myeloid leukaemia by the alpha-emitting nuclides, uranium-233, plutonium-239 and americium-241. Int J Radiat Biol 77, 41 52.

Endo A, Yamaguchi Y and Eckerman KF (2003). Development and assessment of a new radioactive decay database use for dosimetry calculation. Radiat Prot Dosim 105, 565-569.

European Commission (2009). Report of High Level Expert Group on European Low Dose Risk Research. Doi 10.2777/60680.

Feinendegen LE, Paretzke H and Neumann RD (2008). Two principal considerations are needed after low doses of ionizing radiation. Radiat Res 169, 247-48.

Fell TP, Harrison JD and Leggett RW (2001). A modelf or the transfer of alkaline earth elements to the fetus. Radiat Prot Dosim 95, 309-21.

Fill UA, Zankl M, Petoussi-Henss N, Siebert M and Regulla D (2004). Adult female voxel models of different stature and photon conversion coefficients for radiation protection. Health Physics 86, 253-72.

Gilbert ES, et al (2004). Lung cancer in Mayak workers. Radiat Res 162, 505-16.

Grogan HA, Sinclair WK and Voilleque PG (2001). Risks of fatal cancer from inhalation of 239,240plutonium by humans: a combined four-method approach with uncertainty analysis. Health Phys 80, 447-61.

Harrison JD and Muirhead CR (2003). Quantitative comparisons of cancer induction in humans by internally deposited radionuclides and external radiation. Int J Radiation Biology 79, 1-13.

Harrison JD, Fell TP, Phipps AW and Smith TJ (2005). The new ICRP model of the human alimentary tract: target cell assumptions and colon doses from ingested alpha- and beta-emitting radionuclides. Proc 9th Int Conf on Health Effects of Incorporated Radionuclides: Emphasis on Radium, Thorium, Uranium and Their Daughter Products. Neuherberg: GSF, pp.293-300.

Harrison JD and Streffer C (2007). The ICRP protection quantities, equivalent and effective dose: their basis and application. Radiat Prot Dosim 127, 12 8.

Harrison JD and Day P (2008). Radiation doses and risks from internal emitters. J Radiat Prot 28, 137-59.

Harrison JD (2009). Biokinetic and dosimetric modelling in the estimation of radiation risks from internal emitters. J Radiol Prot 29, A81-A105.

HPA (2007). Report of Independent Advisory Group on Ionising Radiation. Review of risks from tritium. Docs of HPA, RCE-4, HPA, Chilton.

HPA (2009). Radon and Public Health. Report of the independent Advisory Group on Ionising Radiation. Docs of HPA, RCE-11, HPA, Chilton.

Hough M, Johnson P, Rajon D, Jokisch D, Lee C and Bolch W ((2011). An image-based skeletal dosimetry model for the ICRP reference adult male – internal electron sources. Phys Med Biol 56(8), 2309-46.

ICRP (1979). Limits for intakes of radionuclides by workers: ICRP Publication 30, Part 1. Annals ICRP 2 (3/4). Pergamon Press, Oxford.

ICRP (1980). Limits for intakes of radionuclides by workers: ICRP Publication 30, Part 2. Annals ICRP 4 (3/4). Pergamon Press, Oxford.

ICRP (1981). Limits for intakes of radionuclides by workers: ICRP Publication 30, Part 3. Annals ICRP 6 (2/3). Pergamon Press, Oxford.

ICRP (1983). Radionuclide transformations. Energy and intensity of emissions. ICRP Publication 38, Ann ICRP 11-14.

ICRP (1988). Limits for Intakes of Radionuclides by Workers: An Addendum. ICRP Publication 30 (Part 4). Ann ICRP 19 (4).

ICRP (1989). Individual Monitoring for Intakes of Radionuclides by Workers. ICRP Publication 54. Ann ICRP 19 (1-3).

ICRP (1990). Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 1. ICRP Publication 56. Ann ICRP 20 (2).

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

ICRP (1993). Age-dependent doses to members of the public from intake of radionuclides: part 2, ingestion dose coefficients. ICRP Publication 67. Ann ICRP 23 (3/4). Elsevier Science Ltd, Oxford.

ICRP (1994a). Human respiratory tract model for radiological protection: ICRP Publication 66. Ann ICRP 24 (1-3). Elsevier Science Ltd, Oxford.

ICRP (1994b). Dose Coefficients for Intake of Radionuclides by Workers: ICRP Publication 68. Ann ICRP 24 (4). Elsevier Science Ltd, Oxford.

ICRP (1995a). Age-dependent doses to members of the public from intake of radionuclides: part 3, ingestion dose coefficients. ICRP Publication 69. Ann ICRP 25 (1). Elsevier Science Ltd, Oxford.

ICRP (1995b). Age-dependent doses to members of the public from intake of radionuclides: part 4, inhalation dose coefficients. ICRP Publication 71. Ann ICRP 25 (1). Elsevier Science Ltd, Oxford.

ICRP (1995c). Age-dependent doses to members of the public from intake of radionuclides: part 5, compilation of ingestion and inhalation dose coefficients. ICRP Publication 72. Ann ICRP 26 (1). Elsevier Science Ltd, Oxford.

ICRP (1996). Conversion Coefficients for use in Radiological Protection against External Radiation. ICRP Publication 74. Ann ICRP 26 (3-4).

ICRP (1997). Individual Monitoring for Internal Exposure of Workers (preface and glossary missing). ICRP Publication 78. Ann ICRP 27 (3-4).

ICRP (2001). Doses to the embryo and fetus from intakes of radionuclides by the mother. ICRP Publication 88. Ann. ICRP 31 (1-3). Elsevier Science Ltd, Oxford. Corrected version issued May 2002.

ICRP (2002b). Basic anatomical and physiological data for use in radiological protection: reference values. ICRP Publication 89. Ann ICRP 32 (3-4). Oxford: Elsevier Science.

ICRP (2003). Relative biological effectiveness (RBE), quality factor (Q), and radiation weighting factor (wR). ICRP Publication 92. Ann ICRP, 33 (4). Elsevier Sciences Ltd, Oxford.

ICRP (2004). Doses to infants from ingestion of radionuclides in mothers' milk. ICRP Publication 95. Ann ICRP 34 (3/4). Elsevier Sciences Ltd, Oxford.

ICRP (2006). Human alimentary tract model for radiological protection. ICRP Publication 100. Ann ICRP 36 (1/2). Elsevier Science Ltd, Oxford.

ICRP (2007). 2007 Recommendations of the International Commission on Radiological Protection. Publication 103. Ann ICRP 37 (2-4). Elsevier Science Ltd, Oxford.

ICRP (2009a). Nuclear decay data for dosimetric calculations. ICRP Publication 107. Ann ICRP 38 (3).

ICRP (2009b). Adult Reference Computational Phantoms. ICRP Publication 110. Ann ICRP 39 (2).

ICRP (2011a). Early and late effects of radiation in normal tissues and organs: threshold doses for tissue reactions and other non-cancer effects of radiation in a radiation protection context (in press).

ICRP (2011b). Statement on Tissue Reactions. www.icrp.org.

Johnson PB, Bahadori AA, Eckerman KF, Lee C and Bolch WE (2011). Response functions for computing absorbed dose to skeletal tissues from photon irradiation – an update. Phys Med Biol 56(8), 2346-65.

Jokisch DW, Bouchet LG, Patton PW, Rajon DA and Bolch WE (2001). Beta-particle dosimetry of the trabecular skeleton using Monte Carlo transport within 3D digital images. Med Phys 28, 1505-18.

Krestinina LY, Preston DL, Ostroumova EV, Degteva MO, Ron E, Vyushkova OV, Stratsev NV, Kossenko MM and Akleyev AV (2005). Protracted radiation exposure and cancer mortality in the Techa River Cohort. Radiat Res 164, 602-11.

Krewski D et al (2006). A combined analysis of North American case-control studies of residential radon and lung cancer. J Toxicol Environ Health A 69, 533-97.

Lee C, Lodwick D, Hurtado J, Pafundi D, Williams JL and Bolch WE ((2010). The UF family of reference hybrid phantoms for computational radiation dosimetry. Phys Med Biol 55(2), 339-63.

Lim FT, Kanhai HH and Falkenburg JH (2005). Characterization of the human CD34+ hematopoietic progenitor cell compartment during the second trimester of pregnancy. Haematological 90, 173-9.

Lubin JH, et al (2004). Risk of lung cancer and residential radon in China: pooled results of two studies. Int J Cancer 109, 132-7.

McGeoghegan D, Binks K, Gillies M, Jones S, and Whaley S (2008). The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946-2005, Int J Epidemiol Jun 37 (3), 506-18.

Medvinsky AL, Samoylina NL, Muller AM and Dzierzak EA (1993). An early pre liver intra-embryonic source of CFU-S in the developing mouse. Nature 364, 64-7.

Metcalf D and Moore MAS (1971). Embryonic aspects of haemopoiesis. Haemopoietic Cells (New York: American Elsevier), pp172-267.

Miller G (2008). Variability and uncertainty of biokinetic model parameters: the discrete empirical bayes approximation. Radiat Prot Dosim 131(3), 394-398.

Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC, and Zhang W (2009). Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. British Journal of Cancer 100, 206-212.

NAS/NRC (2006). Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Board on Radiation Effects Research.

NCRP (2001). Evaluation of the linear-non threshold dose-response model for ionizing radiation. NCRP Report No. 136. Bethesda, MD, National Council on Radiation Protection and Measurements.

Nikjoo H, Bolton CE, Watanabe R, Terrissol M, O'Neill P and Goodhead DT (2002). Modelling of DNA damage induced by energetic electrons (100 eV to 100 keV). Radiat Prot Dosim 99, 77-80.

Phipps AW, Fell TP, Harrison JD, Paquet F and Leggett RW (2007). Dose coefficients calculated using the new ICRP model for the human alimentary tract. Radiat Prot Dosim 127, 79-85.

Preston DL, Shimizu Y, Pierce DA, Suyama A and Mabuchi K (2003). Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and non-cancer disease mortality: 1950-97. Radiat Res 160, 381-407.

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K and Kodama K (2007). Solid cancer incidence in atomic bomb survivors: 1958 1998. Radiat Res 168, 1-64.

Puncher M, Birchall A and Bull RK (2011). Uncertainties on lung doses from inhaled plutonium. Radiat Res (in press).

Raabe OG (2010). Concerning the health effects of internally deposited radionuclides. Health Phys Soc. doi: 10.1097/HP.0b013e3181c20e25.

Shagina NB, Tolstykh EI and Degteva MO (2003). Improvements in the biokinetic model for strontium with allowance for age and gender differences in bone mineral metabolism. Radiat Prot Dosim 105, 619-22.

Shagina NB, Tolstykh EI, Fell TP, Harrison JD, Phipps AW and Degteva MO (2007). In utero and postnatal haemopoietic tissue doses resulting from maternal ingestion of strontium isotopes from the Techa River. Radiat Prot Dosim 127, 497-501.

Shah AP, Jokisch DW, Rajon DA, Watchman CJ, Patton PW and Bolch WE (2005a). Chord-based versus voxel-based methods of electron transport in the skeletal tissues. Med Phys 32, 3151-9.

Shah AP, Bolch WE, Rajon DA, Patton PW and Jokisch DW (2005b). A paired-image radiation transport model for skeletal dosimetry. J Nucl Med 46, 344-53.

Shilnikova NS, et al (2003). Cancer mortality risk among workers at the Mayak nuclear complex. Radiat Res 159, 797-8.

Shimizu Y, Kodama K and Nishi N, et al (2010). Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. Br Med J 340, 5349.

Sokolnikov ME, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV, Vasilenko EK and Koshurnikova NA (2008). Lung, liver and bone cancer mortality in Mayak workers. Int J Cancer 123, 905-11.

Stabin MG, Tagesson M, Thjomas SR, Ljungberg M and Strand SE (1999). Radiation dosimetry in nuclear medicine. Applied Radiation Isotope 50, 73 87.

Tavian M and Peault B (2005a). Embryonic development of the human hematopoietic system. Int J Dev Biol 49, 243-50.

Tavian M and Peault B (2005b). The changing cellular environments of hematopoiesis in human development in utero. Exp Hematol 33, 1062-9.

Tirmarche M, Laurier D, Bochicchio F, Cardis E, Binks K, Hofmann W, Muirhead C and Canu I (2010). Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiologic studies, organ dose calculation and risk assessment. Final scientific report in the Frame of the European project “Alpha Risk” N° 516483, period 2005-2009.

Tolstykh EI, Degteva MO, Vorobiova MI and Kozheurov VP (2001). Fetal dose assessment for the off spring of the Techa Riverside residents. Radiat Environ Biophys 40, 279-86.

Tubiana M, Aurengo A, Averbeck D and Masse R (2008). Low-dose risk assessment: the debate continues. Radiat Res 69, 246-7.

UNSCEAR (2000). 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. United Nations, New York.

UNSCEAR (2006a). United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR 2006 Report to the General Assembly with scientific annexes. Effects of Ionizing Radiation, Vol I: Report to the General Assembly, Scientific Annexes A and B.

UNSCEAR (2006b). United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR 2006 Report to the General Assembly with scientific annexes. Effects of Ionizing Radiation, Vol II: Scientific Annexes C, D and E.

UNSCEAR (2008). Report of the United Nations Scientific Committee on the Effects of Atomic Radiation, 56th Session (July 2008) General Assembly Official Records. New York: United Nations.

UNSCEAR (2011). United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. 2008 Report to the General Assembly with Annexes, Volume II, United Nations, New York.

WHO (World Health Organization, International Agency for Research on Cancer) (2001). IARC Monographs on the Evaluation of Carcinogenic Risk in Humans. Vol. 78, Ionizing Radiation, Part 2: Some Internally Deposited Radionuclides (Lyon: IARC Press).

Wilpshaar J, Joekes EC, Lim FT, Van Leeuwen GA, Van den Boogaard PJ, Kanhai HH, Willemze R and Falkenburg JH (2002). Magnetic resonance imaging of fetal bone marrow for quantitative definition of the human fetal stem cell compartment. Blood 100, 451-7.

Zankl M, Fill U, Petoussi-Henss N and Regulla D (2002). Organ dose conversion coefficients for external photon irradiation of male and female voxel models. Physics Medical Biology 47, 2367-85.

Zankl M, Petoussi-Henss N, Fill U and Regulla D (2003). The application of voxel phantoms to the internal dosimetry of radionuclides. Radiat Prot Dosim 105, 539-48.

Zankl M, Eckerman K and Bolch WE (2007). Voxel-based models representing the male and female ICRP reference adult – the skeleton. Radiat Prot Dosim 127, 174-86.

# 3 PROGRESS IN UNDERSTANDING RADON RISK

**D. Laurier**

*IRSN - Institute for Radiological Protection and Nuclear Safety, France*

## 3.1 Introduction

Radon-222 is a naturally occurring radioactive gas. It is formed as the decay product of radium-226 which is a member of the uranium-238 decay chain. Uranium and radium, naturally present in soil and rocks, provide a continuous source of radon. Radon emanates from the earth's crust and is present everywhere in the air. It can cumulate and reach high concentration in confined places, such as underground caves, mines, or in some closed rooms. Radon concentration in indoor air depends on the geology of the area and factors that affect the pressure differential between the inside and outside of the building, such as ventilation rates, heating within the building and meteorological conditions.

Radon-222 has a half-life of 3.8 days, and decays into a series of solid short-lived radioisotopes (less than half an hour), several of them emitting alpha particles. When radon gas is inhaled, its decay products can deposit in the different part of the lungs, and can lead to an irradiation of the cells. In addition to lung, dosimetric studies indicate that a small part of the dose due to inhalation of radon gas and radon decay products can be delivered to organs other than lung [1]. Radon can also be found in high concentration while dissolved in underground water. Drinking of such ground water supplies may lead to doses to specific organs, especially the digestive tract [1, 2].

Radon has been recognised as a human lung carcinogen in 1988 by the World Health Organisation [3]. The main source of information on risks of radon- induced lung cancer has been epidemiological studies of underground miners [2, 4]. More recently, several studies were developed to analyse lung cancer risk associated to residential radon exposures in the general population.

The historical unit of exposure to radon progeny applied to the uranium mining environment is the working level month (WLM) which is related to the potential alpha energy concentration of its short-lived decay products. One WLM is defined as the cumulative exposure from breathing an atmosphere at a concentration of 1 working level (WL) for a working month of 170 hours. A concentration of 1 WL is any combination of the short-lived radon progeny in one litre of air that will result in the emission of $1.3\ 10^5$ MeV of alpha energy. One WLM is equivalent to $3.54\ 10^{-3}$ J h $m^{-3}$ in SI units. Exposures can also be quantified in terms of the activity concentration of the radon gas in Bq h $m^{-3}$. The two units are related via the equilibrium factor, F, which is a measure of the degree of disequilibrium between radon and its short-lived progeny (1 WLM = $6.37\ 10^5$ / F Bq h $m^{-3}$; 1 J h $m^{-3}$ = $1.8\ 10^8$ / F Bq h $m^{-3}$). Thus, an annual domestic exposure of 227 Bq $m^3$ gives rise to 1 WLM, assuming occupancy of 7000 h $y^{-1}$ and F value of 0.4.

The present paper aims to review the recent results accumulated in the epidemiological literature, especially regarding four directions:

- The demonstration of lung cancer risks associated to low levels of Radon exposure,
- The quantification of the exposure risk relationship, including the impact of modifying factors and the interaction with other lung cancer risk factors,
- The interest of organ dose calculations in the analysis of radon associated risks,
- The determination of potential radon-induced health effects other than lung cancer.

The manuscript distinguishes between lung cancer and non lung cancer effects, and between epidemiologic studies of miners and of the general population. A specific focus is given to results obtained in Europe, especially in the frame of EC collaborative research programs.

## 3.2 Lung cancer risk associated to radon inhalation

### 3.2.1 Miners studies

#### *3.2.1.1 Recent epidemiological studies*

About 20 epidemiologic studies developed since the 60's in populations of miners (uranium, iron, fluorspar, tin) all around the world (Australia, Canada, China, Czech Republic, France, Germany, Sweden, UK, USA). Several comprehensive analyses have been performed that provided coherent results on the existence of an association between cumulative exposure to radon and radon decay products and lung cancer risk [2, 4, 5]. More recently, the UNSCEAR 2006 report provided a comprehensive review of available epidemiological results, including a total of more than 126,000 miners [6]. The weighted mean average Excess Relative Risk (ERR) per 100 WLM was 0.59 (95%Confidence Interval (95%CI) = 0.35-1.0) [6]. A modifying effect of time since exposure (decrease of the ERR with increasing delay since exposure) and of age at exposure (higher ERR for exposures received at young age) on the exposure-risk relationship was observed.

Several studies are still active, in Canada [7, 8], USA [9], Czech Republic [10-12], France [13-16], Germany [17-25], Sweden [26, 27]. Compared to previous analyses, these studies have the advantage to present longer duration of follow-up (important in order to assess the effect of age and time parameters), larger number of miners (important in order to increase the statistical power), better quality of exposure assessment (important in order to improve the precision of the exposure-risk estimates), lower levels of exposure (important in order to derive results pertinent for radiation protection), availability of incidence data (important in order to distinguish between different histological types of lung cancer) or additional information on other risk factors (important in order to control for potential confounders or to estimate the interaction with radon of risk factors such as gamma rays, ore dust, diesel exhaust, silica, smoking).

In Europe, several collaborative research programs were launched to analyse risk associated to radon. We can cite the "U miners+Animal data" project in the frame of the EC framework program 5 (FP5, 2000-2003, contract FIGH-CT1999-0013) [28], and more recently the "Alpha-Risk" project, coordinated by M Tirmarche (IRSN), in the frame of the EC FP6 (2005-2009, contract FI6R-CT-2005-516483). This project included 18 partners from 9 different countries. The final report has been issued at the beginning of 2010 [29] and some publications are still under way. Additional information can be found on http://www.alpha-risk.org. This project enabled the construction of a joint database combining the data from three European cohorts of uranium miners. The pooled European cohort finally included more than 50,000 male miners with a long duration of follow-up (mean 26 years) and individually reconstructed exposures to radon gas and radon decay products, long-lived radioactive ore dust (LLR) and external gamma rays. The low percentage of individuals lost to follow-up (less than 4% in each cohort) indicates the very good quality of the cohorts. Close to 10,000 deaths were recorded, including more than 1500 lung cancer deaths (Table 1). This very large population provided a high statistical power and was able to demonstrate long term health effects linked to relatively low cumulated exposure to alpha emitters.

**Table 1 Characteristics of the uranium miner cohorts involved in the Alpha-Risk European project [29]**

| | France | Czech republic | Germany | Total |
|---|---|---|---|---|
| Population size | 5,086 | 9,979 | 35,084 | 50,149 |
| Employment period | 1946–1989 | 1937–1974 | 1955–1989 | 1937–1989 |
| Follow-up period | 1946–1999 | 1952–1999 | 1955–1998 | 1946–1999 |
| Person-years | 153,047 | 262,507 | 908,661 | 1,324,215 |
| Deaths n (%) | 1,467 (29) | 3,947 (39) | 4,519 (13) | 9,933 (20) |
| Length of follow-up (y)* | 30.1 (>0–53) | 26.3 (>0–48) | 25.9 (>0–43) | 26.4 (>0–53) |
| Age at entry in study (y)* | 28.8 (16–68) | 30.2 (17–68) | 22.7 (13–66) | 24.8 (13–68) |
| Age at end of study (y)* | 58.9 (20–85) | 56.6 (19–85) | 48.6 (15–85) | 51.2 (15–85) |
| Mortality | | | | |
| all causes | 1,467 | 3,947 | 4,519 | 9,933 |
| all cancers | 544 | 1,510 | 1,179 | 3,233 |
| lung cancer | 159 | 922 | 462 | 1,543 |
| Cumulative exposure among exposed miners | | | | |
| Radon (WLM)* | 36.6 (0.03–960.1) | 72.8 (0.1–869.8) | 55.9 (>0–1252.8) | 58.0 (0.03–1253) |
| External gamma (mSv)* | 54.7** (0.2–470.1) | 45.6 (0.7–276.5) | 33.5 (>0–616.2) | 38.0 (>0–616.2) |
| Long lived radionuclides (kBq.m-3.h)* | 1.6** (>0–10.0) | 12.1 (0.2–70.3) | 1.6 (>0–68.5) | 4.1 (>0–70.3) |

* mean (min-max)** available only after 1956, WLM: working level month

#### *3.2.1.2 Estimates of risk at low exposure rates*

Since the UNSCEAR 2006 report [6], several studies provided risk estimates in populations exposed to low levels of exposure. This chapter reviews the estimates of ERR per 100 WLM obtained from simple linear models with no modifying factors, at low levels of exposure rate.

Recent analyses from the French and Czech cohorts have provided risk estimates associated with low levels of exposure and reasonably good quality exposure assessment ("measured exposures"), with values of ERR per 100 WLM being 2.4 (95%CI=1.2-4.8) and 3.4 (95%CI=1.8-7.6), respectively in the French and in the Czech study [12]. In the French sub-cohort of miners employed only after the implementation of radiation protection measures in the mines (sub-cohort of 3303 miners employed after 1956, with mean cumulated exposure of 17 WLM), the estimated ERR per 100 WLM was 2.0, still being significantly different from zero (95%CI=0.91 – 3.65) [16].

The results of a joint analysis of the Czech and French miner cohorts initiated in the frame of the "U miners + Animal data" EC project [28] were published in 2008. This analysis included 10,100 miners with a relatively long follow-up (mean about 24 years) and relatively low levels of cumulative exposure (mean 47 WLM). The estimated ERR per 100 WLM was 1.6 (95%CI = 1.0-2.3) globally and 2.7 (95%CI = 1.7-4.3) when based only on "measured exposures" [12].

The German "Wismut" cohort is the largest cohort of uranium miners world-wide. It includes 58,987 miners, with a follow-up completed up to 2003 (mean follow-up of 34 years) [18, 19, 23-25, 30]. Based on this very large cohort, the estimated ERR per 100 WLM was 0.19 (95%CI = 0.16-0.22) [25]. This estimate appears to be much lower than those obtained in other cohorts, but it has to be noted that this population include miners with very high levels of cumulated exposure (max 3,224, mean 280 WLM), especially among miners employed in the very first years (before 1954). Analyses of sub-cohorts with later employment periods should provide much higher ERR estimates. In the Alpha-Risk project, the Wismut cohort was limited to the 35,084 miners employed only after 1956 (means cumulated exposure 56 WLM). In that

population, the estimated ERR per 100 WLM was 0.41 (95%CI = 0.27-0.55), and the estimated ERR per 100 WLM was even 3.76 (95%CI = 2.13-5.39) when limited to the period after 1976, when assessment of individual exposure was the most precise [29].

In Sweden, a new cohort of 5486 miners employed from 1923 to 1996 in the Malmberget iron ore mine was established (mean cumulative exposure 65 WLM). The estimated ERR per 100 WLM was 2.2 (95%CI = 0.7-3.7) [27].

In the Alpha-Risk project, the overall ERR per 100 WLM estimates in the Czech, French and German cohorts appear substantially different, with a higher estimate obtained in the Czech cohort compared to the two other cohorts (Table 2). Nevertheless, considering only exposure windows with good exposure quality and low exposure rates (since 1953, 1956 and 1967, respectively in the Czech, French and German cohort), the estimated ERR per 100 WLM were much closer and the heterogeneity between the three countries was no longer significant. The resulting exposure-lung cancer risk coefficient in the European combined cohort was ERR per 100 WLM = 2.60 (95%CI= 1.83–3.36) (Table 2). The differences in the estimated ERR/WLM between whole cohorts and period-restricted subsets could reflect the effects of several concomitant factors: better quality of exposure assessment in the later periods, lower exposure rates and shorter time since exposure. Indeed, no substantial differences were seen in the estimated exposure-risk relationship between the three cohorts when temporal and exposure period modifying factors were included in models [29].

**Table 2 Estimates of the excess relative risk (ERR) of lung cancer per 100 working level months (WLM) in the Alpha-Risk project [29]**

| | Whole cohorts | | Low exposure rate period * | |
|---|---|---|---|---|
| Cohort | ERR/ 100 WLM | 95%CI | ERR/ 100 WLM | 95%CI |
| Czech | 1.13 | 0.74–1.53 | 2.14 | 1.21–3.08 |
| French | 0.60 | 0.17–1.03 | 2.11 | 0.78–3.44 |
| German | 0.41 | 0.27–0.55 | 3.76 | 2.13–5.39 |
| Joint - | | | 2.60 | 1.83–3.36 |

Models stratified on birth year and country, using a modified external background rate estimation method – no modifying factors. *Exposures since 1953, 1956 and 1967, respectively in the Czech, French and German cohort

Outside Europe, an updated analysis of miners from the Eldorado cohort has been published [7, 31]. This cohort regroups the Port Hope, Port radium and Beaverlodge cohorts. Overall, the cohort included 17,660 Eldorado uranium workers first employed in 1932–1980 and followed up to 1999. In the total population, the estimated ERR per 100 WLM was 0.55 (95%CI = 0.37-0.7). But when focusing on the Beaverlodge cohort (9498 males miners with mean cumulative exposure of 85 WLM), the estimated ERR per 100 WLM was 0.96 (95%CI = 0.56-1.56) [7].

#### *3.2.1.3 Modifying factors, confounding and interaction*

##### 3.2.1.3.1 Age and time modifying effects

Previous analyses demonstrated the effect of attained age and time since exposure on the relationship between radon exposure and lung cancer risk [2, 5]. This observation was confirmed and reinforced by recent analyses [7, 12, 16, 24, 25, 29, 32].

In the Czech and French joint analysis, a model was developed based on a continuous modifying effect of age at mean exposure and time since mean exposure [12]. As this joint analysis was designed to focus on low levels of exposure, no modifying effect of exposure rate was observed. Compared to previous models, this approach has the advantage to avoid jumps in the estimated relative risk. Figure 1 presents the preferred Czech-French model [12]

compared to the previous reference model of the BEIR VI report [2], when applied to a specific scenario of exposure. The two models are coherent, and indicate a strong decrease of risk with time since exposure, the relative risk being close to 1 (the relative risk of a non-exposed individual) 30 years after the end of exposure.

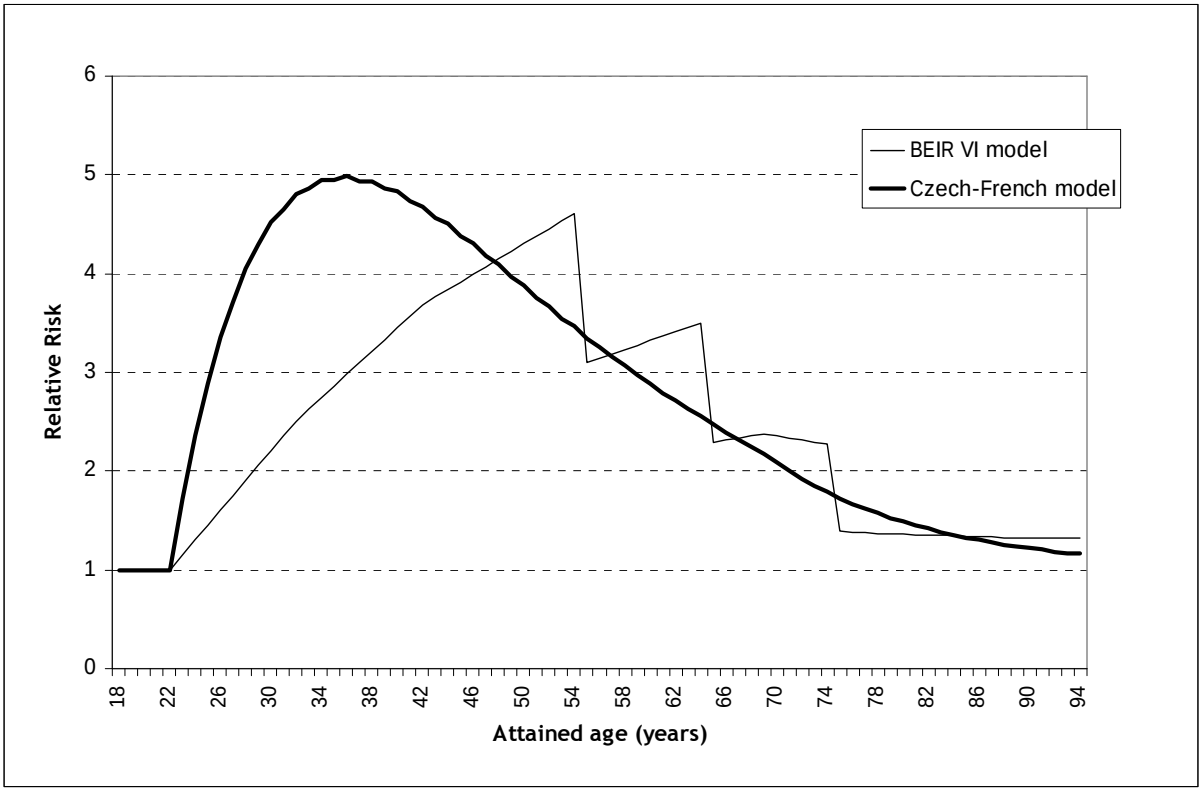



**Figure 1 Relative risk of lung cancer mortality associated to radon exposure* according to the BEIR VI model and to the joint Czech-French model**

BEIR VI model: linear ERR model with modifying effect of attained age, time since exposure and mean radon concentration [2]; Czech-French model: linear ERR model with continuous modifying effect of time since median exposure and age at mean exposure [12]; * continuous exposure to radon decay products at a rate of 2 WLM per year from age 18 to 64.

A similar approach was applied to the German Wismut cohort. The ERR model for lung cancer appeared to be linear in radon exposure, with exponential effect modifiers of age at median exposure, time since median exposure, and radon exposure-rate. The estimated ERR per 100 WLM was 1.06 (95%CI=0.69-1.42) for an age at median exposure of 33 y, a time since median exposure of 11 y, and an exposure-rate of 2.7 WL. The ERR decreased by 5% for each unit exposure-rate increase, by 32% with each decade increase in age at median exposure and by 54% with each decade increase in time since median exposure [25].

A detailed analysis of modifying effects of the exposure-risk relationship was performed in the frame of the Alpha-Risk European project, based on the joint Czech-French-German cohort [29]. All modifying factors identified in the BEIR VI report [2], particularly the effects of time since exposure, attained age, and exposure rate, were found to be similar. The estimated ERR appears very similar in all models, indicating that the different approaches are very coherent in regard to the evaluation of the effect of the exposure-risk modifiers. When the modifiers were included in the models, the estimated ERR per 100 WLM were very similar in the three countries. Among all, the preferred model was based on simultaneous exposure windows based on time since exposure, age at exposure and exposure rate, which are more appropriate in studies of chronic exposure [29].

Another strong modifier appeared to be the period of exposure. Indeed, when separating the whole history of exposure into different periods according to the quality of radon exposure assessment, the ERR per 100 WLM observed for the period with the better quality was much higher than that associated to the other period. This modifying effect was observed in the French cohort [16] and in the Czech cohort [12, 29, 33], but was less or not present in the German cohort [25]. Nevertheless, as periods of better quality of radon exposure assessment are in general recent, this factor is strongly associated with time since exposure and attained age, and the interpretation of these results should be made with caution.

#### 3.2.1.3.2 Interaction with smoking

Smoking is by far the strongest risk factor for lung cancer. Unfortunately most studies of underground miners did not allow reconstructing individual smoking habits. Nevertheless, several studies had partial smoking data, and case-controls studies among miners have also been conducted to investigate the interaction between radon exposure and smoking on lung cancer risk. Available results indicate that the relationship between lung cancer mortality and radon exposure persists when account is taken of smoking habits. The analyses conducted for the BEIR VI report indicated a sub-multiplicative interaction between radon exposure and smoking status [2]. When the smoking status was known, the estimated ERR generally appeared to be larger (even if not significantly) among non-smokers than among smokers [5, 34].

An updated analysis of the Colorado Plateau miners cohort has been recently published [9]. This cohort is particularly interesting as smoking behaviour has been reconstructed for almost all miners (99.8% of the 4137 miners) and presents a high percentage of never smokers (23%, reaching 54% in the American Indian fraction of the cohort). The interaction between radon and smoking in causing lung cancer was estimated to be sub-multiplicative but greater than additive [9].

In a recent French nested case-control study, the ERR for lung cancer related to cumulative radon exposure was still significant when adjusted for smoking, and remained very close to that obtained in the French cohort when smoking information was ignored [35]. The same was observed in a recent nested case-control study implemented in the frame of the German Wismut miners' cohort. The ERR per WLM adjusted on smoking was very similar to the crude risk and to the risk found in the Wismut cohort study [21]. Also in the Czech uranium miners cohort was conducted a nested case-control study. The ERR per WLM adjusted on smoking was very similar to the crude one, and the relative risk from combined effects was lower than multiplicative and higher than additive [10]. This stability of the radon-related lung cancer risks with and without adjustment for smoking suggests that smoking does not act as a major confounder in miners studies.

In the frame of the Alpha-Risk European project, a combined analysis of three case-control studies nested in the three European uranium miner cohorts (Czech, French and German) was performed to study the joint effects of radon exposure and smoking on lung cancer death risk. It was the largest case-control study even conducted among miners. It included 1046 lung cancer cases and 2492 controls with detailed radon exposure data and smoking status. The ERR per 100 WLM adjusted for smoking was 0.8 (95%CI=0.4-1.4), confirming that the lung carcinogenic effect of radon persisted even when smoking was adjusted for [29]. Additional analyses provided arguments in favour of a sub-multiplicative interaction between radon and smoking, even if a multiplicative effect may be possible at low levels of radon exposure [36].

#### 3.2.1.3.3 Other confounders

Miners are exposed to several non-radiological factors present in the mines atmosphere, which could act as confounders of the true relationship between radon exposure and lung cancer risk. Among these, we can list inhalation of fine dust and silica dust, arsenic and diesel exhaust. Several studies developed efforts to reconstruct miners past exposures to these factors and now enable to analyse the potential effect of these factors.

Silica is a well-known lung cancer risk factor. A recent article suggested that exposure to quartz dust may be an important confounder [26], but it finally appeared to account for no more than 10 to 20% of the association observed between radon exposure and lung cancer risk in the Malmberget cohort [27]. In France, a case-control study nested in the French cohort of uranium miners provided an opportunity to take account of silicosis and smoking in the assessment of the relation between radon and lung cancer. If the study revealed a significant association between lung cancer risk and silicosis, the relation between radon and lung cancer persisted after adjusting for smoking and silicotic status [37]. In Germany, exposure to silica dust of Wismut miners has been reconstructed through a job exposure matrix [19, 38]; this should allow very soon an analysis of the potential impact of this confounder in the German Wismut cohort.

Almost no study enabled to consider the potential impact of diesel exhaust on the estimation of lung cancer risk among miners. Diesel exhaust is generally considered as modest in the mines. A recent analysis in Sweden concluded that it should not be a major confounder in the studies of lung cancer and radon exposure [26, 39].

### *3.2.1.4 Calculation of lung doses*

Up to now, all analyses of lung cancer risk associated to radon relied on exposure estimates (in WLM). Nevertheless, several recent works provide information on the corresponding dose to the lung.

Recent dosimetric analyses suggest that smoke-induced morphological and physiological changes in the lung can modify the doses of inhaled radon progeny compared to non-smokers. For the same exposure, doses higher by about a factor of 2 were estimated for heavy long-term smokers than for non-smokers. Authors concluded that the contribution of inhaled radon progeny to the risk of lung cancer in smokers may be higher than currently assumed [40].

Leonard suggested that, due to variations of humidity and aerosol median diameter, dose may decrease with exposure rate. According to him, such variations of doses may explain the lung cancer risk inverse exposure-rate effect observed for in several studies [41].

In addition to radon gas and radon decay products, uranium miners are also exposed to external gamma radiation and to LLR. These two sources of exposures were considered as negligible in the early years, but this is less true in the recent years. Furthermore, these radiological exposures are generally highly correlated, making it difficult to discriminate the impact of each component on the lung cancer risk [42].

One main aim of the Alpha-Risk European project was to analyse the risk of death from cancer in uranium miners in relation to the organ dose due to these three sources of exposure. This work relied on a tight collaboration between epidemiologists and dosimetrists. Data on exposure to radon gas, radon decay products, gamma radiation and LLR were available for the French, Czech and German cohorts. Significant correlations between the three exposures were observed in each cohort. A large amount of work was done to characterize the mines atmosphere for different periods since the beginning of uranium extraction, to determine

specific work-type profiles, and to propose pertinent parameters for the dosimetric calculation. The calculation relied on the implementation of ICRP models, taking into account the specificities of exposures in mines atmospheres. The Alpha Miner software was developed specifically for that study [43, 44]. This software was then applied to each miner form the European joint cohort to estimate the absorbed organ doses (in Gray) due to each of the four exposure components. For lung, the absorbed dose was essentially attributable to radon progeny; the contribution of this component to the total absorbed dose varied between 58 and 86% according to the cohort (between 93 and 97% in equivalent dose (in Sievert), applying a weighting factor of 20 to alpha particles). A preliminary analysis of the dose-risk relationship between cumulated equivalent organ dose and lung cancer risk showed a positive and significant ERR/Sv = 0.07 (95%CI=0.06–0.08). Positive and significant ERR were also observed for non-alpha and alpha lung doses. Nevertheless, total dose being due essentially to radon progeny, the authors concluded that this component was responsible for most of the excess risk observed among the European uranium miners [29]. More detailed analyses are ongoing, especially to consider different weighting factors for alpha particles. The quantification of uncertainties associated to dose calculation also constitutes a major research topic for the future [45].

The conversion of radon exposure (WLM) into effective dose (Sv) is still being debated. The ICRP calculated doses from radon and its progeny using a dose conversion convention based on miner epidemiological studies, referred to as the epidemiological approach [4, 46], whereas the UNSCEAR defined a dose coefficient from dosimetric models and epidemiological studies [6, 47]. Despite these different approaches, differences between conversion factors are only about 10 to 30%, which is negligible when compared with the uncertainty associated with both dosimetric and epidemiological studies [48]. Currently, an update of the ICRP conversion convention using risk estimates based on the most recent epidemiological data would yield values that are in good agreement with dose calculation, using ICRP biokinetic and dosimetric models (dosimetric approach). The ICRP now proposes to treat radon progeny in the same way as other radionuclides and to publish dose coefficients calculated using dosimetric models, for use within the ICRP system of protection. Such dose coefficients should be proposed by the ICRP in near future [49].

#### *3.2.1.5 Assessment of lifetime risks*

Due to the demonstrated existence of time modifying factors of the relationship between cumulated radon exposure and lung cancer risk, such as age at exposure or time since exposure, the comparison of results between different miner studies or with indoor studies is difficult. Calculation of lifetime risk estimates associated with a specific exposure scenario could allow taking account of these variations [50]. This approach was used in the International Commission for Radiation Protection Publication 65 to estimate the risk of lung cancer associated with prolonged exposure to radon concentrations based upon studies of underground miners [4]. Since that, several lifetime risk estimates have been published [2, 51, 52], but with various underlying assumptions about lifetime duration or background rates.

The ICRP recently updated the estimation of lifetime excess absolute risk (LEAR) of lung cancer death from radon and radon progeny, considering results accumulated since the ICRP Publication 65 [4]. Based especially on results obtained with the BEIR VI model [2] and the Czech-French model [52], a LEAR of about $5\ 10^{-4}$ per WLM ($14\ 10^{-5}$ per mJ h $m^{-3}$) was derived. The ICRP concluded that this value should now be used as the nominal probability coefficient for radon and radon progeny induced lung cancer [53]. This new value will replace the previous value of $2.8\ 10^{-4}$ per WLM ($8\ 10^{-5}$ per mJ h $m^{-3}$) published in the ICRP Publication 65 [4]. In addition to this assessment, a sensitivity analysis was performed; it showed that the estimated LEAR can vary from about 3 to $7\ 10^{-4}$ per WLM according to the model used [54]. Other calculations also illustrated the sensitivity of LEAR estimates to background rates (according to the country or to the proportion of smokers).

### 3.2.2 Indoor studies

#### *3.2.2.1 Pooled analyses*

The use of results from underground miners to estimate radon-induced lung cancer for residential concentrations of radon has been an important issue over the last twenty years. Indeed, this transposition implies several strong hypotheses (extrapolation to low levels of exposure, transposition from a specific working group to the general population, analogy between exposures in the mining atmosphere and in the homes). In order to provide direct information on risks associated with domestic radon concentrations, more than 20 residential epidemiological studies were launched in the late 1980s and early 1990s in different countries. A number of European studies were designed with the intention of conducting a pooled analysis. Several large case-control studies were also conducted in the USA, in Canada and in China. A comprehensive review of these studies has been published in the UNSCEAR 2006 report [6]. Except one cohort study conducted in the Czech Republic [55], all studies used case-control designs. Information about past individual histories was collected retrospectively from questionnaires, for the cases (lung cancer patients) and the controls (non lung cancer patients of the same age and sex, from the same hospital or from the general population). This information generally included family and personal medical history, potential occupational exposures, residential history, and a detailed reconstruction of smoking habits. Radon exposure was reconstructed through the use of dosimeters in previous housings, generally over a period of 20 to 30 years before the diagnosis.

Between 2004 and 2007, three pooled analyses have been published, based on data from China [56], North America [57, 58] and Europe [59, 60] (Table 3). These pooled analyses considered individual basic data and applied standard methodologies, both in defining selection criteria and in the statistical analyses. Thanks to their large numbers of individuals, these joint analyses provided a much larger statistical power to detect a potential association between radon exposure and lung cancer risk if it exist. Each of these three joint analyses observed an increase of lung cancer risk with increasing indoor radon concentration over the last 20 to 30 years prior to diagnosis (with a 5-year lag time). Lung cancer risk estimates per unit of exposure in the three joint analyses were very close to each other, with ERR estimates varying between 8 and 13% per 100 Bq.m$^{-3}$. Limiting the European analysis to those cases and controls with a relatively low annual exposure, there is convincing evidence of an increased risk for those exposed to levels below 200 Bq m$^{3}$. An increase in risk is observed among smokers as well as among non-smokers [60].

**Table 3 Pooled analyses of case-control studies of lung cancer risk associated to indoor radon**

| Pooled analysis | Number of studies included | Average exposure*in Bq m$^{-3}$ | Number of cases | Number of controls | Relative risk per 100 Bq m$^{-3}$ (95% CI) |
|---|---|---|---|---|---|
| European [60] | 13 | 105 | 7,148 | 14,208 | 1.08 (1.03-1.16) |
| North American [58] | 7 | 67 | 3,662 | 4,966 | 1.10 (0,99-1.26) |
| Chinese [56] | 2 | 201 | 1,050 | 1,995 | 1.13 (1.01-1.36) |

CI: confidence interval *: over the period 5-30 years before diagnosis

In the European pooled analysis, taking account of random uncertainties in radon measurements increased the estimates relative risk from 1.08 to 1.16 per 100 Bq.m$^{-3}$ [60]). Limiting the analysis to residents with at least 20-year coverage of measurements over the 5-30 years period before diagnosis, the estimated relative risk was 1.21 per 100 Bq.m$^{-3}$ and 1.32

per 100 Bq.m$^{-3}$, respectively in the North American pooled study and in the Chinese pooled study [56, 58].

Extensive analyses of these results have been performed, which also concluded that these results are highly coherent in demonstrating the existence of an increased risk of lung cancer associated to radon exposure in homes [61, 62]. Risk estimates obtained from indoor epidemiological studies are now sufficiently robust to enable protection of the public to be now based on residential concentration levels [53, 62].

A “world pooling” analysis is currently in progress. This study should include the data already considered in the three pooled analyses presented below, and the data of three additional studies. Globally, this new pooled analysis should include more than 13,700 lung cancer cases. This very large size will provide a large statistical power to quantify the risk of lung cancer associated to radon exposure in houses, and should allow specific analyses in specific subgroups such as non-smokers.

#### *3.2.2.2 Assessment of attributable risks*

##### 3.2.2.2.1 Lifetime risk estimates

On the basis of the results of the European pooling, several authors estimated the lifetime risk of lung cancer. In the UK, the cumulative risk of lung cancer up to age 75 for a lifelong non-smoker is estimated to be 0.4%, 0.5% and 0.7% for radon activity concentrations of 0, 100 and 400 Bq m$^{-3}$, respectively. In comparison, the cumulative risk of lung cancer up to age 75 for a lifelong smoker is estimated to be 10%, 12% and 16%, respectively for the same radon concentrations [60, 61]). These estimates reflect the dominating effect of tobacco use on lifetime risk of lung cancer with or without radon contribution. If the relative risk of lung cancer associated to radon exposure appears to be similar among non-smokers than among smokers (miner studies even observed higher relative risks among non-smokers), the absolute risk of lung cancer remains much higher among smokers than among non-smokers.

The comparison of results obtained from miner studies and from indoor studies is not straightforward, and may be misleading. This is due mainly to the use of different epidemiological designs (mostly cohort studies for miners and case-control studies for indoor exposures) as well as different measures of exposure (WLM in mines, Bq.m$^{-3}$ in homes). The miner studies have the advantage of considering the evolution over time of the individual radon cumulative exposure and therefore enable the consideration of the modifying effects of age and time since exposure, but often are unable to consider the effect of cofactors, such as smoking. The domestic case-control studies have the advantage of providing detailed information about many potential cofactors, but contemporary measures must be used to estimate prior radon concentrations during previous decades. They generally consider only the average radon concentration in a home over a given period and are not able to analyse potential time modifiers of the exposure-risk relationship. Nevertheless, several authors tried to compared the estimated risk coefficients obtained from indoor studies with those derived from miners studies, with more or less elaborated approaches, and they generally concluded that these estimates were coherent [6, 29, 33, 52, 60, 63].

A recent comparison has been performed using lifetime risk calculation based on a given scenario of exposure. This approach can allow considering the modifying effects of age and time since exposure on the exposure-risk relationship demonstrated by miner studies. The estimated lifetime risks estimated using models from the pooled miner studies (the BEIR VI study [2] and the French-Czech joint study [12]) or from the European indoor pooled analysis where less than 30% different [53, 54]. The currently available results therefore show a good consistency between lung cancer risk estimates obtained from miner and from indoor studies.

#### 3.2.2.2.2 Attributable fraction

On the basis of these risk coefficients, the number of lung cancers attributable to radon exposure can be estimated. Such calculations have been performed in several countries. Results depend on the estimated level of indoor radon concentration, on the lung cancer background rate, on the proportion of smokers, and on the choice of the risk model (model derived from miners studies of from indoor studies). A review of published results has been performed recently by WHO. The percentages of lung cancer attributable to radon vary from 3 to 14% according to the country [62]. Nevertheless, these estimates of the burden of lung cancer caused by indoor radon are associated to very large uncertainties, and should be considered with caution only as elements to orientate public health decisions.

It must also be noted that these attributable fractions correspond to the whole collective exposure to radon. But radon exposure being log normally distributed, only a small fraction of the population lives in houses with high radon exposures. For example in France, it has been estimated that about 3 to 12% of all lung cancer deaths could be globally attributed to radon exposure in houses (arithmetic mean concentration of 87 $Bq.m^{-3}$). But, 47% of this attributable fraction is associated to houses with concentration below 100 $Bq.m^{-3}$ (76% of the population), and only 9% of this attributable fraction is associated to houses with concentration above 400 $Bq.m^{-3}$ (2% of the population) [64]. The same reasoning has been conducted in the UK. It has been estimated that about 3 to 12% of all lung cancer deaths could be globally attributed to radon exposure in houses (arithmetic mean concentration of 21 $Bq.m^{-3}$), but around 70% of these attributable deaths are estimated to occur following exposure to radon concentrations of less than 50 $Bq.m^{-3}$, and only 3-4% to radon concentrations of more than 200 $Bq.m^{-3}$ [61]. The cost effectiveness of radon mitigation therefore depends on the mean concentration, and recommendations will vary between countries [65-67]. Calculations performed in the frame of the Alpha-Risk project on the basis of alternative exposure scenarios indicated that, even for persons in their 50s, radon mitigation in their homes could have a notable impact on their lifetime risk of radon-induced lung cancer mortality [29]. The available knowledge on radon risks clearly indicates today that regulation is needed to diminish lung cancer risk in houses with elevated radon concentration, but in addition some preventive measures against radon in new homes should be recommended in order to decrease the mean exposure.

## 3.3 Non-lung cancer risks potentially associated to radon inhalation

Radon and its progeny deliver substantially greater dose to the lung than to systemic organs and the gastrointestinal tract regions. Nevertheless, calculations indicate that small doses may be received by the red bone marrow (RBM) and other systemic organs [1, 68-70].

### 3.3.1 Miners studies

#### *3.3.1.1 Calculation of organ doses*

In miner studies, radon exposure is expressed in WLM. This unit does not allow separating the contribution of the gas and of the decays products to radon exposure. As lung dose is due essentially to radon decay products, WLM appears as a good indicator to estimate radon associated lung cancer risk. But radon gas contributes significantly to the dose received by other tissues and, depending, on the value of the equilibrium factor, the proportion of the two components could be different, which would have an impact on the estimated dose to organs other than lung [71-74].

Miners are also exposed to external gamma radiation and to LLR from ore dust, but only a few cohorts allowed considering these exposures. They contribute to the dose, and may confound the assessment of the relationship between radon exposure and the risk of death from causes other than lung cancer among miners [74]. These different factors can lead to important uncertainties associated to dose estimates [73, 75]. Consideration of the composite nature of the exposures and of the associated uncertainties is an important point in the estimation of the risks other than lung cancer among miners.

Assessment of organ-specific absorbed doses associated to chronic exposures to radon gas, radon decay products, external gamma rays and LLR was a main objective of the Alpha-Risk European project [29]. In this framework, the Alpha Miner was used to estimate absorbed and equivalent doses to lung, kidney, liver and red bone marrow for each miner from the European joint cohort [44]. This work allowed quantifying the respective contribution of each source of exposure to organ doses (alpha and non-alpha) [43]. Further studies are needed to quantify and reduce uncertainty in the estimation of the organ doses and to quantify the impact of this uncertainty in the estimated dose-risk relationship.

#### *3.3.1.2 Recent epidemiological results*

##### 3.3.1.2.1 Solid cancers other than lung

Studies of underground miners have generally not shown any excess of cancer other than lung cancer to be associated with radon exposure [2, 6, 76].

An excess of larynx cancer suggested in early analyses was not confirmed in recent studies [77, 78]. Specific excesses were noted by recent studies for non-Hodgkin lymphoma, multiple myeloma [9], kidney [15], stomach or liver [20] but such observations have not been confirmed by other studies and no consistent pattern has emerged.

Recent analyses of the German Wismut miners cohort showed a small but statistically significant relationship with cumulative radon exposure for all extra-pulmonary cancers (ERR per 100 WLM=0.014 (95%CI=0.006–0.023)) [20]. This association appeared to be linear with radon exposure, with a modifying effect of attained age (the ERR decreased by 37% with each decade increase in attained age) [24]. A specific analysis was also performed for stomach cancer risk, on the basis of organ dose calculations, taking into account of the contribution of radon gas, radon decay products, external gamma rays and LLR. A Significant increase in risk of death from stomach cancer with increasing absorbed dose was observed, with ERR per Gy = 1.53 (95%CI=0.23-2.73). Nevertheless, after adjustment for arsenic and fine dust exposure, this association was no more significant (ERR per Gy = 0.40; 95%CI=-1.06 -1.86) [79].

##### 3.3.1.2.2 Leukaemia

Because ionizing radiation is a known risk factor for leukaemia, it has been hypothesized that radon might increase the risk of leukaemia in humans. Nevertheless, for a given level of radon exposure, the estimated dose to RBM is about 100 times lower than the estimated dose to lung [1]. Moreover, interpretation of results from miner studies is generally complicated due to low numbers of cases and potential confounding by external gamma radiation and inhalation of ore dust.

A joint analysis of 11 miner cohorts from various countries was published in 1995. Despite its very large size, this pooled analysis included only 69 leukaemia deaths. A significantly elevated risk of death from leukaemia appeared, but only for those miners who had worked

less than 10 years. No association was observed between cumulated exposure to radon and leukaemia mortality [76].

A retrospective case-cohort study performed among Czech uranium miners concluded to an association between the incidence of all leukaemia combined and cumulative radon exposure (based on 84 cases). Chronic lymphocytic leukaemia (CLL) alone also appeared to be significantly linked to radon (based on 53 CLL cases). The authors indicated that similar associations were noted with external gamma exposure, but no analysis was performed to consider simultaneously the different components of the dose [80].

In the Czech cohort of uranium miners, a significant excess of leukaemia mortality was observed compared to the general population (based on 30 leukaemia deaths). The analysis used the estimated equivalent RBM dose due to radon gas, radon progeny, external gamma radiation and inhalation of uranium ore dust. Results showed that the increased mortality was mainly observed decades after exposure. The increased risk of leukaemia among uranium miners was significantly associated with cumulated equivalent RBM dose, but the dose was dominated by exposures to long lived alpha radionuclides in airborne particulates (more than 60%) and radon contributed to less than 10% [11].

An individually matched case-control study of leukaemia risk was conducted on the basis of the medical archives of former uranium miners in East Germany. The study included 377 leukaemia cases and 980 controls. The results suggested that an elevated risk for leukaemia was restricted to employees with a very long occupational career in underground uranium mining or uranium processing. No association between exposure to short-lived radon progeny and leukaemia risk was observed [81]. A new analysis of the same dataset was recently performed, using an enhanced dose calculation method and taking into account doses from medical chest x-ray examinations [82]. The absorbed RBM dose was calculated considering both occupational (radon and its short-lived progeny, LLR and external gamma radiation) and diagnostic exposures. The percentage of the total absorbed RBM dose arising from radon inhalation was about 31% (28% from gas and 3% from radon progeny). A moderately elevated (but not statistically significant) risk was seen in the dose category above 200 mGy [82].

A preliminary analysis of leukaemia risk was performed in the frame of the Alpha-Risk European project. Globally, a significant excess of leukaemia mortality was observed in the pooled French-Czech-German cohort (based on 69 leukaemia deaths), due mainly to the excess observed in the Czech cohort. RBM dose was calculated from radon gas, radon decay products, LLR and external gamma radiation, using the Alpha miner software [44]. A weighting factor of 20 was used to estimate equivalent dose. A significant association between leukaemia risk and the equivalent RBM dose was observed, with an ERR per Sv = 3.7 (95%CI=1.1–8.8). Positive and significant ERR were also observed for non alpha and alpha RBM doses. When considering separately CLL and non-CLL, both were positively associated to total equivalent RBM doses [29, 83]. Contrarily to the lung, the contribution of radon progeny to RBM was negligible whereas the contribution of radon gas was more important. Together, radon gas and radon decay products contributed to approximately 40% of the total RBM dose. This makes it difficult to conclude about the real association between radon and leukaemia risk.

In conclusion, some evidence of increased risk of leukaemia among miner cohorts emerged in the recent years. This increased risk seems to be associated to a long duration of exposure, and an association with RBM dose is observed, but a link with radon exposure is not confirmed.

#### 3.3.1.2.3 Circulatory system diseases

Cohorts of miners generally show no excess of circulatory system diseases (CSD). The Newfoundland fluorspar miner cohort study found an elevated death rate from coronary heart diseases among miners with high cumulative radon exposure, but this finding was based on a relatively small number of deaths and was not statistically significant [84]. Reanalysis of this cohort with ten additional years of follow-up showed no association between radon exposure and mortality from CSD, acute myocardial infarction, or cerebrovascular disease [85]. A recent analysis of the German Wismut uranium miner cohort did not find any trend with increasing cumulative exposure to radon neither for the risk of death from CSD, nor for more precise diagnoses (heart disease or stroke) [18, 86]. An excess of myocardial infarction mortality has been observed in the Swedish mines of Malmberget and Kiruna, but an association with radon exposure was not tested [87]. In the recent analysis of the Eldorado cohort in Canada, no association was observed between radon exposure and ischemic heart disease or other cardiovascular disease. A negative association was even noted for stroke [7].

In the French cohort of uranium miners, a detailed analysis of CSD mortality was recently performed. The cohort comprised 5086 miners, followed up for a mean duration of 30.1 years, with a low level of radon cumulated exposure (mean 37 WLM). No excess risk was found overall for CSD mortality (based on 319 deaths), but a significant positive trend with cumulative radon exposure was observed for cerebrovascular diseases, with an ERR per 100 WLM=0.49 (95%CI=0.07–1.23) [13]. Nevertheless, due to the lack of data about known cardiovascular risk factors, these findings should be interpreted very cautiously.

### 3.3.2 Indoor studies

#### *3.3.2.1 Recent epidemiological results*

Epidemiological studies have been conducted to evaluate the possible association between leukaemia and indoor radon concentrations. For childhood leukaemia, an association with domestic radon exposure has been observed in some ecological studies [88-90]. Several large-scale case-control studies which included alpha-track measurements in the homes of all subjects were unable to confirm an association between radon exposure and leukaemia risk [91-93]. This absence of result may be due to methodological limits, such as a lack of statistical power, insufficient geographical variation in the RBM dose, too large number of missing data, participation bias, imprecise individual estimates of exposure, lack of control for potential confounders (such as terrestrial gamma exposure for example) [94].

A nationwide case-control study including 1153 leukaemia cases and 2306 controls has recently been conducted in Denmark [95]. Residential radon concentrations were calculated from a model based on a previous measurement programme and a number of explanatory variables such as house type and geology [96]. These model predictions of radon concentrations in homes avoid the bias potentially associated with limited participation, which has been a major problem in several previous studies. This study observed a positive significant association between radon concentrations and childhood acute lymphocytic leukaemia (ALL), with an estimated ERR per 1000 $Bq.m^{-3}.y$ of 0.56 (95%CI=0.05 – 1.30) [95]. An additional work suggested that air pollution from traffic may enhance the effect of radon on the risk of childhood leukaemia, but the authors admitted that this observation could be a chance finding and this association remains highly hypothetical [97].

A recent review concluded that an association between indoor exposure to radon and childhood leukaemia might exist, but the current epidemiological evidence is weak and further research with better study designs is needed [94]. In Great Britain, it was estimated that a large study (nationwide recruitment of cases over 10 or 20 years) should have sufficient power

to detect the predicted risk attributable to natural background radiation. The authors recommend the choice of a case-control study design, and the use of dose prediction models to avoid participation bias associated to individual consent requirement [98]. Nevertheless, in their dose estimations, radon contributed to only 6% of the total RBM dose attributable to natural sources of radiation in Great Britain, and the capacity of an epidemiological study to distinguish the effect of radon from that of other sources of exposure should therefore be very low.

Several studies are ongoing in Europe (UK, France, Switzerland). Especially, the CCRG-HPA study (Childhood Cancer Research Group and Health Protection Agency) in the UK and the GEOCAP study (Inserm and IRSN) in France are large nationwide projects using both measured and predicted exposure values and should provide more insight on the association between natural background radiation (including radon) and the risk of leukaemia among childhood in the coming years.

#### *3.3.2.2 Assessment of attributable risks*

Several authors evaluated the fraction of childhood leukaemia that could be attributed to radon exposure from the results observed in epidemiological studies. From their ecological study conducted in France (mean concentration 85 $Bq.m^{-3}$), Evrard et al estimated that 5.4% (95%CI=0.01%-11.3%) of childhood acute leukaemia cases could be attributed to radon exposure [88]. From their case-control study conducted in Denmark (population-weighted average annual radon concentration 59 $Bq.m^{-3}$), Raaschou-Nielsen et al estimated that about 9% of childhood ALL cases could be attributed to radon exposure [95].

Conventional assessments of attributable risk have also been made, using dose-risk relationships from the literature (generally derived from the results from the Hiroshima and Nagasaki survivors follow-up) and estimates of the RBM equivalent dose. As a rough estimate, it has been suggested in 2004 that about 6% of fatal childhood leukaemia cases might be attributed to radon in the United Kingdom [69]. In a more recent work, the estimated average equivalent dose due to natural sources of exposure in Great Britain was estimated to be about 1.3 mSv per annum for children less than 15 [98]. Using these dose estimates, the authors estimated that natural exposure may account for 15 to 20% of all cases of childhood leukaemia in Great Britain, although the uncertainties associated with this estimate are considerable [99, 100]. Given that radon contributes only to about 10% of the dose, one can estimate the fraction attributable to radon exposure to about 2% (0.5 to 3% according to the model). According to these calculations, the authors concluded that it is unlikely that radon could detectably influence the risk of childhood leukaemia in Great Britain (in regard to other sources of background radiation) [101]. Nevertheless, the situation may be different in other countries with higher radon concentrations (and then a higher contribution of radon to RBM dose).

Conventional dose assessments are based on systemic models, in which the dose derives from the transfer of radon gas from inhalation or ingestion to the circulatory system and to cells close to RBM. An alternative route has been recently postulated, according to which an additional contribution may be due to dose received from radon and its decay products by circulating lymphocytes while present in the tracheo-bronchial epithelium [102]. However, as circulating lymphocytes spend only a limited time within the tracheo-bronchial epithelium, this hypothesis seems unlikely to be of importance for the risk of childhood leukaemia.

## 3.4 Risks potentially associated to radon in drinking water

Whereas lung cancer risk following radon inhalation is strongly established, much less is known about a possible health effect of radon ingestion via drinking water [103]. While the concentration in surface water is generally very low, radon in underground water or in some wells can reach very high concentrations, up to several hundred or thousands of $Bq.L^{-1}$ [2]. The highest dose from radon ingestion is received by the stomach wall. After absorption, radon gas can enter the blood circulation, and could deliver doses to several organs, such as liver, RBM, brain, kidney or intestine [2]. Contrarily to the situation for lung and radon inhalation, the dose due to radon ingestion will be dominated by radon gas for most organs [1, 69].

Only few epidemiological studies provided results on health risks associated to radon in drinking water. They considered stomach cancer, but also leukaemia, kidney, central nervous system and colon. No convincing pattern of risk emerged from the available studies [104]. Most studies used geographical designs. Only one cohort study has been carried out in Finland to study the association between bedrock well water radioactivity and cancer. Three case-cohort studies were nested into this cohort, considering respectively stomach cancer [105], urinary cancer [106], and leukaemia [107]. None of these studies reported significant association, either with radionuclide concentrations in well water (uranium, radium and radon were examined in each study) or with cumulative radiation doses when estimated [106].

Important methodological limitations affect most of the reviewed studies. These limitations are due to study design (only few studies with individual data), exposure measurement methods (poor characterisation of exposure), and control for confounding factors or sample size. Inhalation of airborne radon exhaled from soils or water constitutes by far the most important route of exposure to this radionuclide, and drinking water reflects only part of the exposure routes. In addition, external exposure to telluric gamma rays was not considered in any of the reviewed studies.

In conclusion, it appears that the currently available results do not allow quantifying the health effects of radon in water [104]. Nevertheless, it seems that cancer risk posed by radon in household public water supply is small and can mainly be attributed to the transfer of radon into air and the subsequent inhalation of radon decay products, rather than to ingestion of water. The risk could however be higher for people using private wells for water supply where radon levels could be high and variable [108].

## 3.5 Conclusions and perspectives

### 3.5.1 Conclusions

Recent results from miner epidemiological studies provided precise estimates of lung cancer risk associated to radon cumulated exposure. Risk coefficients provided by these low-level exposure studies are generally higher than those previously published. The differences in the estimated ERR/WLM between whole cohorts and period-restricted or level-restricted subsets could reflect the effects of several concomitant factors: better quality of exposure assessment in the later periods, lower exposure rates and shorter time since exposure.

Recent results from miner epidemiological studies also allowed a better quantification of modifying factors of the exposure-risk relationship and of the interaction with smoking. Results confirm the major effect of time since exposure and of age at exposure. The relationship between radon exposure and lung cancer risk appears to be only little modified after controlling for smoking.

Consideration of these recent results from miner studies led to an increase of the estimated lifetime lung cancer absolute risk attributable to radon compared to previous ICRP estimates.

There is compelling evidence from cohort studies of underground miners and from case-control studies of residential radon exposures that radon and its progeny can cause lung cancer. Comparisons of relative risk estimates between miners and residential models yielded very coherent estimates.

Collaborative works between epidemiologists and dosimetrists allowed calculation of lung dose-risk relationships (instead of exposure-risk models previously). This approach allowed considering the contribution of radon gas, radon decay products, external gamma radiation and LLR to lung dose. Results demonstrated the existence of a radiation induced lung cancer risk among miners, and confirmed the major contribution of exposure to radon decay products to the organ dose.

For solid tumours other than lung cancer, and also for leukaemia, there is currently no consistent evidence of any excess associated with radon and radon progeny exposures. Nevertheless, more concern is put on this issue in regards to recently published results from both miner studies or from studies of childhood leukaemia.

### 3.5.2 Perspectives

International collaboration is indispensable in order to demonstrate risks at low doses. Major progresses in the understanding of radon risks in the last 10 years derived from international collaborative research project, such as the European Alpha-Risk project for miners or the European pooling project for indoor studies. Continuation of such efforts should be supported in the future. We can cite the Euro-Can initiative, which aims to gather data from miner studies in Europe (Czech, French and German) and in Canada. Also, for residential studies, the "World pooling project" is currently in progress, and should include data from almost all indoor radon case-control studies in the world.

Regarding the quantification of the relationship between radon exposure and lung cancer risk, some progress should be obtained in the near future from the consideration of uncertainties and measurement errors associated to radon exposure. Several works on this specific issue are ongoing, both on miner and residential data.

The collaborative approach initiated in the recent years between epidemiologists and dosimetrists appears as a very promising way. Several results deriving from this approach should be published in the coming years. Further studies are needed to quantify and reduce uncertainty in the estimation of the organ doses and to quantify the impact of this uncertainty in the estimated dose-risk relationship.

The conversion of radon exposure (WLM) into effective dose (Sv) is still being debated. The ICRP now proposes to treat radon progeny in the same way as other radionuclides and to publish dose coefficients calculated using dosimetric models, for use within the ICRP system of protection. Such dose coefficients should be proposed by the ICRP in near future.

Several results published during the last years raised the issue of risks other than lung cancer potentially associated to radon. Answer to this issue requests very long follow-up periods and good control for potential confounders. The extension of the follow-up of current miner cohorts should provide new elements regarding this issue in the next 10 years.

It is noted that most available data relate to adult population. While dosimetric calculations indicate that doses per unit exposure should not differ appreciably between children and adults, more information is needed to quantify the effects of exposures received during

childhood. Several studies are ongoing in Europe that should provide more insight on the association between natural background radiation (including radon) and the risk of leukaemia among childhood in the coming years.

The development of molecular epidemiology studies is also a promising orientation for research. The identification of biomarkers could allow better classification of individuals regarding exposures, or provide early indicators of diseases or discrimination of sensitive individuals. Several initiatives have already been launched among German [30] or Czech miners [109]. Interdisciplinary collaborative research programs, gathering epidemiologists, dosimetrists and biologists should be supported to provide new knowledge on radon associated risks in the next decades.

## 3.6 Acknowledgements

I want to thank Eric Blanchardon, Olivier Laurent, Klervi Leuraud, Estelle Rage and Margot Tirmarche from the IRSN for their careful reading of this manuscript and for their constructive comments. This manuscript largely refers to results from the Alpha-Risk European research project, which was supported by the European Commission (2006-2009, EC FP6, contract FI6R-CT-2005-516483).

## 3.7 References

[1] Kendall GM, Smith TJ. Doses to organs and tissues from radon and its decay products. J Radiol Prot. 2002 Dec;22(4):389-406.

[2] National Research Council. Committee on Health Risks of Exposure to Radon. Board on Radiation Effects Research. Health effects of exposure to radon. BEIR VI report. Washington, D.C.: National Academy Press 1999.

[3] International Agency for Research on Cancer. Monographs on the Evaluation of Carcinogenic Risk to Humans: Manmade Fibres and Radon. Lyon: International Agency for Research on Cancer 1988.

[4] International Commission of Radiological Protection. Protection against Radon-222 at home and at work. ICRP Publication 65: Annals of the ICRP vol 23(2) 1993.

[5] Lubin J, Boice JD, Edling JC, Hornung W, Howe G, Kunz E, et al. Radon and lung cancer risk: A joint analysis of 11 underground miner studies: National Institutes of Health (NCI) 1994.

[6] United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR 2006, Annexe E “Sources-to-effects assessment for radon in homes and workplaces. New York.: United Nations 2009.

[7] Lane RS, Frost SE, Howe GR, Zablotska LB. Mortality (1950-1999) and Cancer Incidence (1969-1999) in the Cohort of Eldorado Uranium Workers. Radiat Res. 2010 Oct;174:773-85.

[8] Villeneuve PJ, Morrison HI, Lane R. Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. Health Phys. 2007 Feb;92(2):157-69.

[9] Schubauer-Berigan MK, Daniels RD, Pinkerton LE. Radon exposure and mortality among white and American Indian uranium miners: an update of the Colorado Plateau cohort. Am J Epidemiol. 2009 Mar 15;169(6):718-30.

[10] Tomasek L. Interaction of radon and smoking among Czech uranium miners. Radiat Prot Dosimetry. 2010:in press.

[11] Tomasek L, Malatova I. Leukaemia and Lymphoma Among Czech Uranium Miners. Medical Radiology and Radiation Safety. 2006;51(5):74-9.

[12] Tomasek L, Rogel A, Tirmarche M, Mitton N, Laurier D. Lung cancer in French and Czech uranium miners: Radon-associated risk at low exposure rates and modifying effects of time since exposure and age at exposure. Radiat Res. 2008 Feb;169(2):125-37.

[13] Nusinovici S, Vacquier B, Leuraud K, Metz-Flamant C, Caer-Lorho S, Acker A, et al. Mortality from circulatory system diseases and low-level radon exposure in the French cohort study of uranium miners, 1946-1999. Scand J Work Environ Health. 2010 Sep;36(5):373-83.

[14] Rage E. The French cohort of Uranium miners. Taipei International Forum for global health 22 april 2010; Taipei Medical University.

[15] Vacquier B, Caer S, Rogel A, Feurprier M, Tirmarche M, Luccioni C, et al. Mortality risk in the French cohort of uranium miners: extended follow-up 1946-1999. Occup Environ Med. 2008 Sep;65(9):597-604.

[16] Vacquier B, Rogel A, Leuraud K, Caer S, Acker A, Laurier D. Radon-associated lung cancer risk among French uranium miners: modifying factors of the exposure-risk relationship. Radiat Environ Biophys. 2009 Feb;48(1):1-9.

[17] Grosche B, Kreuzer M, Kreisheimer M, Schnelzer M, Tschense A. Lung cancer risk among German male uranium miners: a cohort study, 1946-1998. Br J Cancer. 2006 Nov 6;95(9):1280-7.

[18] Kreuzer M, Grosche B, Schnelzer M, Tschense A, Dufey F, Walsh L. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946-2003. Radiat Environ Biophys. 2010 May;49(2):177-85.

[19] Kreuzer M, Schnelzer M, Tschense A, Walsh L, Grosche B. Cohort profile: the German uranium miners cohort study (WISMUT cohort), 1946-2003. Int J Epidemiol. 2010 Aug;39(4):980-7.

[20] Kreuzer M, Walsh L, Schnelzer M, Tschense A, Grosche B. Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960-2003. Br J Cancer. 2008 Dec 2;99(11):1946-53.

[21] Schnelzer M, Hammer GP, Kreuzer M, Tschense A, Grosche B. Accounting for smoking in the radon-related lung cancer risk among German uranium miners: results of a nested case-control study. Health Phys. 2010 Jan;98(1):20-8.

[22] van Dillen T, Dekkers F, Bijwaard H, Kreutze M, Grosche B. Lung Cancer from Radon: A Two-Stage Model Analysis of the WISMUT Cohort, 1955-1998. Radiat Res. 2010 Oct 5: online pub.

[23] Walsh L, Dufey F, Mohner M, Schnelzer M, Tschense A, Kreuzer M. Differences in baseline lung cancer mortality between the German uranium miners cohort and the population of the former German Democratic Republic (1960-2003). Radiat Environ Biophys. 2010 Sep 25: online pub.

[24] Walsh L, Dufey F, Tschense A, Schnelzer M, Grosche B, Kreuzer M. Radon and the risk of cancer mortality--internal Poisson models for the German uranium miners cohort. Health Phys. 2010 Sep;99(3):292-300.

[25] Walsh L, Tschense A, Schnelzer M, Dufey F, Grosche B, Kreuzer M. The influence of radon exposures on lung cancer mortality in German uranium miners, 1946-2003. Radiat Res. 2010 Jan;173(1):79-90.

[26] Bergdahl IA, Jonsson H, Eriksson K, Damber L, Jarvholm B. Lung cancer and exposure to quartz and diesel exhaust in Swedish iron ore miners with concurrent exposure to radon. Occup Environ Med. 2010 Aug;67(8):513-8.

[27] Jonsson H, Bergdahl IA, Akerblom G, Eriksson K, Andersson K, Kagstrom L, et al. Lung cancer risk and radon exposure in a cohort of iron ore miners in Malmberget, Sweden. Occup Environ Med. 2010 Aug;67(8):519-25.

[28] Tirmarche M, Laurier D, Bergot D, Billon S, Brueske-Hohlfeld I, Collier C, et al. Quantification of lung cancer risk after low radon exposure and low exposure rate: synthesis from epidemiological and experimental data. Final scientific report, February 2000- July 2003. Contract FIGH-CT1999-00013. Brussels: European Commission DG XII; 2003.

[29] Tirmarche M, Laurier D, Bochicchio F, Cardis E, Binks K, Hofmann W, et al. Final scientific report of the Alpha Risk Project (web site: http://www.alpha-risk.org) funded by the European Commission EC FP6 (ref. FI6R-CT-2005-516483). Brussels: European Commission DG XII; 2010.

[30] Kreuzer M, Grosche B, Dufey F, Schnelzer M, Tschense A, Walsh L. The German Uranium Miners Cohort Study (Wismut cohort), 1946–2003. Technical Report (http://www.bfs.de/en/bfs/forschung/Wismut). Oberschleissheim: Bundesamt für Strahlenschutz February 2010.

[31] Howe GR. Updated analysis of the Eldorado uranium miner's cohort: Part I of the Saskatchewan uranium miner's cohort study. New York: Columbia university; 2006. Report No. RSP-0205.

[32] Tomasek L, Laurier D, Vacquier B, Tirmarche M, Kreuzer M, Tschense A, et al. Radon associated lung cancer risk among European uranium miners – modifying effects of time since exposure and age at exposure. 36th annual meeting of the European Radiation Research Society; 2008 sept; Tours.

[33] Tomasek L, Laurier D, Kreuzer M. Lung cancer risk from occupational and residential radon comparison of detriments. 6th Conference on Protection Against Radon at Home and at Work; 2010 13-17 september; Prague 2010.

[34] Tomášek L. Czech miner studies of lung cancer risk from radon. J Radiol Prot. 2002 Sep;22(3A):A107-12.

[35] Leuraud K, Billon S, Bergot D, Tirmarche M, Caër S, Quesne B, et al. Lung cancer risk associated to exposure to radon and smoking in a case-control study of French uranium miners. Health Phys. 2007;92(4):371-8.

[36] Leuraud K, Schnelzer M, Tomasek L, Kreuzer M, Laurier D. A combined analysis of three European studies on the joint effects of radon exposure and smoking on lung cancer risk among uranium miners. 3rd European IRPA 14-18 june 2010; Helsinki.

[37] Amabile JC, Leuraud K, Vacquier B, Caer-Lorho S, Acker A, Laurier D. Multifactorial study of the risk of lung cancer among French uranium miners: radon, smoking and silicosis. Health Phys. 2009 Dec;97(6):613-21.

[38] Taeger D, Krahn U, Wiethege T, Ickstadt K, Johnen G, Eisenmenger A, et al. A study on lung cancer mortality related to radon, quartz, and arsenic exposures in German uranium miners. J Toxicol Environ Health A. 2008;71(13-14):859-65.

[39] Dahmann D, Bauer HD, Stoyke G. Retrospective exposure assessment for respirable and inhalable dust, crystalline silica and arsenic in the former German uranium mines of SAG/SDAG Wismut. Int Arch Occup Environ Health. 2008 Aug;81(8):949-58.

[40] Baias PF, Hofmann W, Winkler-Heil R, Cosma C, Duliu OG. Lung dosimetry for inhaled radon progeny in smokers. Radiat Prot Dosimetry. 2010 Feb;138(2):111-8.

[41] Leonard BE. Examination of underground miner data for radon progeny size reduction as cause of high radon "inverse" dose rate effect. Health Phys. 2007 Aug;93(2):133-50.

[42] Vacquier B, Rage E, Leuraud K, Caër-Lorho S, Acker A, Laurier D. Lung cancer and multi-exposure to radon, gamma rays and long-lived radionuclides among the post-55 cohort of French uranium miners. 21st EPICOH conference; 2010 20 – 25 april; Taipei; 2010.

[43] Marsh J, Nosske D, Gregoratto D, Karcher K, Blanchardon E, Birchall A, et al. Dosimetric calculations for uranium miners exposed to radon gas, radon progeny and long-lived radionuclides. 3rd European IRPA; 2010 14-18 june; Helsinki; 2010. p. S04-1.

[44] Marsh JW, Bessa Y, Birchall A, Blanchardon E, Hofmann W, Nosske D, et al. Dosimetric models used in the Alpha-Risk project to quantify exposure of uranium miners to radon gas and its progeny. Radiat Prot Dosimetry. 2008;130(1):101-6.

[45] Winkler-Heil R, Hofmann W, Marsh J, Birchall A. Comparison of radon lung dosimetry models for the estimation of dose uncertainties. Radiat Prot Dosimetry. 2007;127(1-4):27-30.

[46] International Commission of Radiological Protection. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103: Annals of the ICRP 37(2–4) 2007.

[47] United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Sources and effects of ionizing radiation - Volume II, Effects. New York: United Nations 2000.

[48] Blanchardon E, Laurier D, Paquet F, Lecomte JF, Tirmarche M. Dosimétrie du radon: les points de vue de l'UNSCEAR et de la CIPR sont-ils contradictoires ? Radioprotection. 2009;44(2):207-16.

[49] Marsh JW, Harrison JD, Laurier D, Blanchardon E, Paquet F, Tirmarche M. Dose conversion factors for radon: recent developments. Health Phys. 2010 Oct;99(4):511-6.

[50] Thomas D, Darby S, Fagnani F, Hubert P, Vaeth M, Weiss K. Definition and estimation of lifetime detriment from radiation exposures: principles and methods. Health Phys. 1992 Sep;63(3):259-72.

[51] Environmental Protection Agency. Assessment of risks from radon in homes. Washington, D.C.: EPA Office of Air and Radiation 2003.

[52] Tomasek L, Rogel A, Laurier D, Tirmarche M. Dose conversion of radon exposure according to new epidemiological findings. Radiat Prot Dosimetry. 2008;130(1):98-100.

[53] International Commission of Radiological Protection. Lung cancer risk from radon and radon progeny. Report of the ICRP Taskgroup 64 (chair: M tirmarche). Draft report for consultation (ICRP ref 4843-4564-6599 1), online http://new.icrp.org/ (July 27 2010): Annals of the ICRP 2010.

[54] Laurier D, Tomasek L, Leuraud K, Tirmarche M. Radon associated lifetime risk. 3rd European IRPA 14 - 18 june 2010; Helsinki.

[55] Tomasek L, Muller T, Kunz E, Heribanova A, Matzner J, Placek V, et al. Study of lung cancer and residential radon in the Czech Republic. Cent Eur J Public Health. 2001 Aug;9(3):150-3.

[56] Lubin JH, Wang ZY, Boice JD, Jr., Xu ZY, Blot WJ, De Wang L, et al. Risk of lung cancer and residential radon in China: pooled results of two studies. International journal of cancer. 2004 Mar;109(1):132-7.

[57] Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidemiology 2005 Mar;16(2):137-45.

[58] Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. J Toxicol Environ Health A. 2006 Apr;69(7):533-97.

[59] Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. Bmj. 2005 Jan 29;330(7485):223.

[60] Darby S, Hill D, Deo H, Auvinen A, Barros-Dios JM, Baysson H, et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. Scand J Work Environ Health. 2006;32 Suppl 1:1-83.

[61] Advisory Group on Ionising Radiation. Radon and public health. Report of the independent Advisory Group on Ionising Radiation: Health protection Agency; 2010.

[62] World Health Organization. Handbook on indoor radon: a public health perspective: World Health Organization, Zeeb, H. and Shannoun, F. Eds 2009.

[63] Zielinski JM, Carr Z, Krewski D, Repacholi M. World Health Organization's International Radon Project. J Toxicol Environ Health A. 2006 Apr;69(7):759-69.

[64] Catelinois O, Rogel A, Laurier D, Billon S, Hemon D, Verger P, et al. Lung cancer attributable to indoor radon exposure in France: impact of the risk models and uncertainty analysis. Environ Health Perspect. 2006 Sep;114(9):1361-6.

[65] Gray A, Read S, McGale P, Darby S. Lung cancer deaths from indoor radon and the cost effectiveness and potential of policies to reduce them. Bmj. 2009;338:a3110.

[66] Haucke F. The cost effectiveness of radon mitigation in existing German dwellings--a decision theoretic analysis. Journal of environmental management. 2010 Nov;91(11):2263-74.

[67] Menzler S, Piller G, Gruson M, Rosario AS, Wichmann HE, Kreienbrock L. Population attributable fraction for lung cancer due to residential radon in Switzerland and Germany. Health Phys. 2008 Aug;95(2):179-89.

[68] Harrison JD, Muirhead CR. Quantitative comparisons of cancer induction in humans by internally deposited radionuclides and external radiation. Int J Radiat Biol. 2003 Jan;79(1):1-13.

[69] Kendall GM, Smith TJ. Doses from radon and its decay products to children. J Radiol Prot. 2005 Sep;25(3):241-56.

[70] Khursheed A. Doses to systemic tissue from radon gas. Radiatiation Protection Dosimetry. 2000;88(2):171-81.

[71] Eatough JP. Radon and leukemia risk in underground miners: are working level months the most appropriate exposure parameter? Health Phys. 2004 Apr;86(4):425-6.

[72] Laurier D, Rogel A, Valenty M, Tirmarche M. Discussion on radon and leukemia risk in underground miners: are working level months the most appropriate exposure parameter? Health Phys. 2004 Apr;86(4):427-8.

[73] Puskin JS, James AC. Radon exposure assessment and dosimetry applied to epidemiology and risk estimation. Radiat Res. 2006 Jul;166(1 Pt 2):193-208.

[74] Tomasek L. Leukemia among uranium miners--late effects of exposure to uranium dust? Health Phys. 2004 Apr;86(4):426-7.

[75] Duport P. Is the radon risk overestimated? Neglected doses in the estimation of the risk of lung cancer in uranium underground miners. Radiat Prot Dosimetry. 2002;98(3):329-38.

[76] Darby SC, Whitley E, Howe GR, Hutchings SJ, Kusiak RA, Lubin JH, et al. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. J Natl Cancer Inst. 1995 Mar 1;87(5):378-84.

[77] Laurier D, Tirmarche M, Mitton N, Valenty M, Richard P, Poveda S, et al. An update of cancer mortality among the French cohort of uranium miners: extended follow-up and new source of data for causes of death. Eur J Epidemiol. 2004;19(2):139-46.

[78] Mohner M, Lindtner M, Otten H. Ionizing radiation and risk of laryngeal cancer among German uranium miners. Health Phys. 2008 Dec;95(6):725-33.

[79] Kreuzer M, Marsh J, Dufey F, Grosche B, Gregoratto D, Nosske D, et al. Ionizing radiation and mortality from stomach cancer Results of the German uranium miners cohort study, 1946-2003. 3rd European IRPA 14 - 18 june 2010; Helsinki. p. S04-1

[80] Rericha V, Kulich M, Rericha R, Shore DL, Sandler DP. Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. Environ Health Perspect. 2006 Jun;114(6):818-22.

[81] Mohner M, Lindtner M, Otten H, Gille HG. Leukemia and exposure to ionizing radiation among German uranium miners. Am J Ind Med. 2006 Apr;49(4):238-48.

[82] Mohner M, Gellissen J, Marsh JW, Gregoratto D. Occupational and diagnostic exposure to ionizing radiation and leukemia risk among German uranium miners. Health Phys. 2010 Sep;99(3):314-21.

[83] Tomasek L, Rage E, Laurier D, Leuraud K, Grosche B, Kreuzer M, et al. Leukaemia risk among European uranium miners in dependence on doses from radon, external gamma, and long lived radionuclides. 3rd European IRPA 14 - 18 june 2010; Helsinki.

[84] Villeneuve PJ, Morrison HI. Coronary heart disease mortality among Newfoundland fluorspar miners. Scand J Work Environ Health. 1997 Jun;23(3):221-6.

[85] Villeneuve PJ, Lane RS, Morrison HI. Coronary heart disease mortality and radon exposure in the Newfoundland fluorspar miners' cohort, 1950-2001. Radiat Environ Biophys. 2007 Aug;46(3):291-6.

[86] Kreuzer M, Kreisheimer M, Kandel M, Schnelzer M, Tschense A, Grosche B. Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946-1998. Radiat Environ Biophys. 2006 Sep;45(3):159-66.

[87] Bjor B, Burstrom L, Eriksson K, Jonsson H, Nathanaelsson L, Nilsson T. Mortality from myocardial infarction in relation to exposure to vibration and dust among a cohort of iron-ore miners in Sweden. Occup Environ Med. 2010 Mar;67(3):154-8.

[88] Evrard AS, Hemon D, Billon S, Laurier D, Jougla E, Tirmarche M, et al. Ecological association between indoor radon concentration and childhood leukaemia incidence in France, 1990-1998. Eur J Cancer Prev. 2005 Apr;14(2):147-57.

[89] Evrard AS, Hemon D, Billon S, Laurier D, Jougla E, Tirmarche M, et al. Childhood leukemia incidence and exposure to indoor radon, terrestrial and cosmic gamma radiation. Health Phys. 2006 Jun;90(6):569-79.

[90] Laurier D, Valenty M, Tirmarche M. Radon exposure and the risk of leukemia: a review of epidemiological studies. Health Phys. 2001 Sep;81(3):272-88.

[91] Steinbuch M, Weinberg CR, Buckley JD, Robison LL, Sandler DP. Indoor residential radon exposure and risk of childhood acute myeloid leukaemia. Br J Cancer. 1999 Nov;81(5):900-6.

[92] Lubin JH, Linet MS, Boice JD, Jr., Buckley J, Conrath SM, Hatch EE, et al. Case-control study of childhood acute lymphoblastic leukemia and residential radon exposure. J Natl Cancer Inst. 1998;90(4):294-300.

[93] UKCCS. The United Kingdom Childhood Cancer Study: objectives, materials and methods. Br J Cancer. 2000;82(5):1073-102.

[94] Raaschou-Nielsen O. Indoor radon and childhood leukaemia. Radiat Prot Dosimetry. 2008;132(2):175-81.

[95] Raaschou-Nielsen O, Andersen CE, Andersen HP, Gravesen P, Lind M, Schuz J, et al. Domestic radon and childhood cancer in Denmark. Epidemiology 2008 Jul;19(4):536-43.

[96] Andersen CE, Raaschou-Nielsen O, Andersen HP, Lind M, Gravesen P, Thomsen BL, et al. Prediction of $^{222}$Rn in Danish dwellings using geology and house construction information from central databases. Radiat Prot Dosimetry. 2007;123(1):83-94.

[97] Brauner EV, Andersen CE, Andersen HP, Gravesen P, Lind M, Ulbak K, et al. Is there any interaction between domestic radon exposure and air pollution from traffic in relation to childhood leukemia risk? Cancer Causes Control. 2010 Nov;21(11):1961-4.

[98] Little MP, Wakeford R, Lubin JH, Kendall GM. The statistical power of epidemiological studies analyzing the relationship between exposure to ionizing radiation and cancer, with special reference to childhood leukemia and natural background radiation. Radiat Res. 2010 Sep;174(3):387-402.

[99] Little MP, Wakeford R, Kendall GM. Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation. J Radiol Prot. 2009 Dec;29(4):467-82.

[100] Wakeford R, Kendall GM, Little MP. The proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionizing radiation. Leukemia. 2009 Apr;23(4):770-6.

[101] Wakeford R. Epidemiology of childhood leukaemia and ionising radiation. Radiation Protection. 2010;163:35-44.

[102] Harley NH, Robbins ES. Radon and leukemia in the Danish study: another source of dose. Health Phys. 2009 Oct;97(4):343-7.

[103] Améon R, Agarande M, Blanchardon E, Canu I, Laurent O, Loyen J, et al. Le radon dans l'eau. Fontenay aux Roses: Institut de Radioprotection et de Sûreté Nucléaire, Rapport DRPH/DIR n°2010-013; 2010.

[104] Laurent O, Guseva-Canu I, Blanchardon E. Conséquences dosimétriques et sanitaires de l'ingestion de radon dans l'eau de boisson. Radioprotection. 2010;45:in press.

[105] Auvinen A, Salonen L, Pekkanen J, Pukkala E, Ilus T, Kurttio P. Radon and other natural radionuclides in drinking water and risk of stomach cancer: a case-cohort study in Finland. International journal of cancer. 2005 Mar 10;114(1):109-13.

[106] Kurttio P, Salonen L, Ilus T, Pekkanen J, Pukkala E, Auvinen A. Well water radioactivity and risk of cancers of the urinary organs. Environmental research. 2006 Nov;102(3):333-8.

[107] Auvinen A, Kurttio P, Pekkanen J, Pukkala E, Ilus T, Salonen L. Uranium and other natural radionuclides in drinking water and risk of leukemia: a case-cohort study in Finland. Cancer Causes Control. 2002 Nov;13(9):825-9.

[108] Al-Zoughool M, Krewski D. Health effects of radon: a review of the literature. Int J Radiat Biol. 2009 Jan;85(1):57-69.

[109] Zölzer F, Hon Z, Navratil L, Rosina J, Skopek J. Micronuclei in lymphocytes of former and current uranium miners. European Radiation Research meeting 5-9 September 2010; Stockholm.

# 4 THORIUM-232, THE LESS KNOWN DECAY CHAIN

**Serena Risica, Francesco Bochicchio and Cristina Nuccetelli**

***Department Technology and Health,***
***Istituto Superiore di Sanità (National Institute of Health),***
***viale Regina Elena 299, Rome, Italy***

## 4.1 Introduction

The thorium chain has undoubtedly been less studied than the uranium chain, and its health effects (e.g. of $^{220}$Rn compared to $^{222}$Rn) have been sometimes underestimated. This is due to several well-known reasons:

- The discovery of radioactivity (and subsequent research efforts) concerned the U series.
- In nuclear energy production, the uranium cycle is much more developed and diffused than the thorium cycle.
- In environmental matrices, activity concentration of $^{238}$U is generally higher than the activity concentration of $^{232}$Th.
- Several nuclides in the thorium chain are more difficult to measure and trace.
- $^{222}$Rn (of the $^{238}$U chain) is the most significant for population dose, whereas $^{220}$Rn is significant in limited areas.
- $^{220}$Rn risk is often believed to be negligible.
- No epidemiological data are available for exposures to $^{220}$Rn, etc.

In the following, couples of radionuclides will be compared: $^{232}$Th *versus* $^{238}$U (because they are both parent nuclides), $^{228}$Ra *versus* $^{226}$Ra, and $^{220}$Rn *versus* $^{222}$Rn. Owing to the limited time, we will just give some flashes and analyse population exposure only, even though $^{232}$Th and $^{220}$Rn are important sources of occupational exposure in NORM industries as well.

## 4.2 $^{232}$Th *versus* $^{238}$U

Thorium is estimated to be three times more abundant in the earth's crust than uranium. It occurs in nature almost entirely as the isotope 232, while uranium is present primarily as the isotope 238 (Eisenbud, 1987). Therefore, in soil the concentration of $^{232}$Th is generally higher than that of $^{238}$U, but owing to the higher specific activity of $^{238}$U, the activity concentration of $^{238}$U is higher than that of $^{232}$Th. However, the $^{232}$Th *population weighted average activity concentration* in soil is 1.4 times that of $^{238}$U (UNSCEAR, 2000, confirmed in UNSCEAR 2008). Indeed, the UNSCEAR *Global Survey on Exposures to Natural Radiation* showed that the reported ratio of $^{238}$U to $^{232}$Th activity concentration in soil is lower than 1 in large parts of the world, e.g. India, China and the Russian Federation, and in the European Member States Finland, Portugal, Romania and Slovakia (see Fig.IX, and table A1 in UNSCEAR, 2008).

Population exposure to the $^{232}$Th or $^{232}$Th series originates mainly from external γ irradiation and intake with the diet.

As for external γ irradiation, it is significant in indoor environments where building materials contain non-negligible activity concentrations of natural radionuclides.

In order to predict this exposure, several models (the so-called *room models*) have been developed and published in international literature. With these models, the absorbed dose rate in air due to γ radiation can be calculated from the activity concentration of $^{238}$U, $^{232}$Th and $^{40}$K in building materials. A comparison of these models, with the geometry of a typical room (4 x 5 x 2.8 $m^3$), showed (Risica et al, 2001) two interesting results: 1) the *specific dose rates*, i.e., the ratios of the dose rate in air to the activity concentration of each nuclide, obtained from different models is comparable; 2) the specific dose rate of the $^{232}$Th series is 1.2 times higher than that of the $^{238}$U series, on average.

In some areas - e.g. of Italy and China - $^{232}$Th activity concentration in building material is higher than that of $^{238}$U: in these cases the $^{232}$Th series can be responsible for high percentages of the total γ dose. In an investigation carried out in Central Italy (Nuccetelli and Bolzan, 2001), in areas where $^{232}$Th activity concentration in building material was about 1.4 times that of $^{238}$U, $^{232}$Th series contribution to the absorbed dose rate in air was about 60%, whereas 25% was attributable to the $^{238}$U series and 15 % to $^{40}$K.

A recent analysis of average values of mean activity concentrations in bricks in European Member States (MS) showed (Trevisi et al., 2008) that $^{232}$Th prevails in the bricks used in several countries (10 MS out of 22), and the average $^{232}$Th activity concentration, calculated on all MS, is higher than that of $^{238}$U, generally represented by its decay product $^{226}$Ra (see tab.1).

**Table 1 Mean activity concentration of $^{226}$Ra, $^{232}$Th and $^{40}$K in bricks of 22 Member States (Trevisi et al., 2008)**

| N. of samples | Activity concentration in bricks (Bq $kg^{-1}$) | | |
|---|---|---|---|
| | $^{226}$Ra | $^{232}$Th | $^{40}$K |
| 1537 | 48 (2 – 200) | 52 (1 – 200) | 619 (12 – 2000) |

However, a more accurate analysis (unpublished as yet), that accounts for the distribution of measurements, shows that they are actually statistically equal. In any case, this means that surveys and research into the $^{232}$Th chain, currently considered of secondary importance, deserve deeper consideration (Nuccetelli and Risica, 2008), also in view of the fact that the $^{232}$Th series is more effective in producing the γ dose indoors.

As regards the possible intake of $^{238}$U and $^{232}$Th with the diet, scarce data are available for $^{238}$U and even less for $^{232}$Th, and few countries have conducted representative national surveys (UNSCEAR, 2000, UNSCEAR, 2008).

Population doses from $^{232}$Th in the diet seem to be generally negligible (UNSCEAR, 2000, UNSCEAR, 2008), but ingestion dose coefficients of $^{232}$Th for all age classes are up to an order of magnitude higher than those of $^{238}$U (ICRP, 1996). Therefore, new investigations should be recommended, because accumulation phenomena cannot be excluded in some environmental matrices, and the knowledge is essential of background values for natural radionuclides in both environmental matrices and biological fluids of unexposed people, as the Chernobyl accident and the London $^{210}$Po poisoning event have clearly shown.

## 4.3 $^{228}$Ra *versus* $^{226}$Ra

Main pathways of population exposure to $^{226}$Ra and $^{228}$Ra are diet and drinking water.

Ingestion dose coefficients of $^{228}$Ra for all age classes are up to one order of magnitude higher than for $^{226}$Ra (ICRP, 1996) (see tab. 2), and relevant doses, particularly from $^{228}$Ra, may be non-negligible in certain situations. Notwithstanding this fact, very scarce data are available on $^{228}$Ra activity concentration in the diet and drinking water (UNSCEAR, 2000, UNSCEAR, 2008). Therefore, representative national surveys would be recommendable, not only to estimate natural background values and the average annual population intake more accurately, but also to highlight possible critical exposures.

In table 2 it can also be noted that $^{228}$Ra ingestion dose coefficients for children and adolescents are 5 to 8 times higher than those for adults; those for infants (≤ 1 year) more than 40 times higher (ICRP, 1996). Therefore, the lower mean volume of drinking water consumed by these age classes (a factor of 2 or 3, as reported in WHO Guidelines (WHO, 2004)), does not compensate for the higher dose coefficients (Risica and Grande, 2000). This means that great caution should be used when implementing these guidance levels for these age classes.

**Table 2 Ingestion dose coefficients for members of the public (ICRP, 1996)**

| Nuclide | Committed effective dose per unit intake (Sv/Bq) | | | | | |
|---|---|---|---|---|---|---|
| | Age class (y) | | | | | |
| | ≤ 1 | 1 - 2 | 2 - 7 | 7 - 12 | 12 – 17 | > 17 |
| $^{226}$Ra | $4.7\ 10^{-6}$ | $9.6\ 10^{-7}$ | $6.2\ 10^{-7}$ | $8.0\ 10^{-7}$ | $1.5\ 10^{-6}$ | $2.8\ 10^{-7}$ |
| $^{228}$Ra | $3.0\ 10^{-5}$ | $5.7\ 10^{-6}$ | $3.4\ 10^{-6}$ | $3.9\ 10^{-6}$ | $5.3\ 10^{-6}$ | $6.9\ 10^{-7}$ |

An example of a non-negligible exposure to $^{226}$Ra and $^{228}$Ra activity concentrations in drinking water was highlighted during a Twinning Project between Estonia and Italy, carried out within the framework of the Estonian Transition Facility Programme, sponsored by the European Union (Forte et al., 2010). Aim of the project was to estimate the radiological situation of Estonian groundwater and related health consequences. Significant $^{226}$Ra and $^{228}$Ra activity concentrations were found especially in the Cambrian-Vendian (Cm-V) aquifer, a large and quite deep (200-400 m) aquifer, the deepest in Estonia that becomes shallower (90-100 m) near the coastal area. The reasons for the high radium concentrations found in these aquifers are discussed in (Forte et al., 2010). In Northern Estonia aqueducts are mainly supplied by this aquifer, therefore doses were assessed by assuming a continuous and exclusive use of water from this aquifer for part of the population of Northern Estonia.

Effective doses were calculated for different age classes using the ICRP dose coefficients (tab.2) and the WHO assumptions on drinking water consumption (WHO, 2004). In table 3, the average doses for adults and infants are reported, together with the average relative contributions of the two radium isotopes to the total dose. The large majority of this dose is due to $^{228}$Ra, particularly for infants (≤ 1 y), despite the similar activity concentrations of the two radium isotopes. This is because the ingestion coefficients of $^{228}$Ra is higher than that of $^{226}$Ra (tab. 2).

The parametric value of 0.1 mSv/y of the Total Indicative Dose (TID), set by the *Council Directive on the quality of water intended for human consumption* (EC 1998), is exceeded by the average effective doses of both adults and infants in these Cm-V waters.

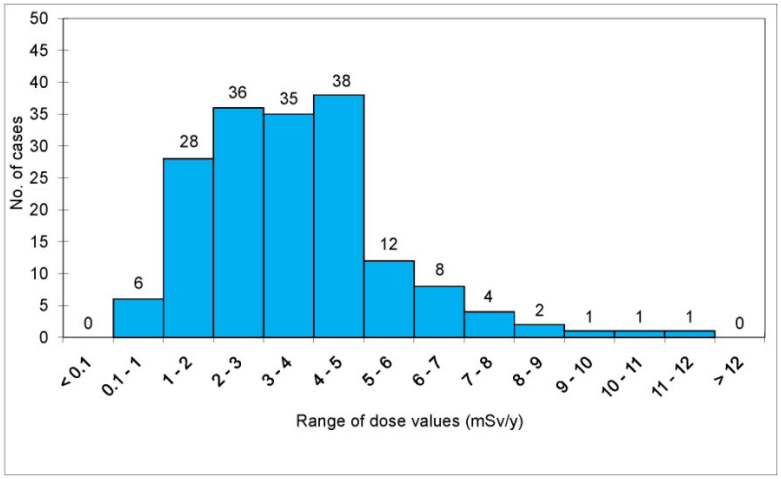
The distribution of doses for infants is summarized in figure 1, where the "numbers of cases" regards the number of wells measured, not the population served. The figure shows that infants ingesting Cm-V water always receive doses higher than the parametric value of 0.1 mSv/y, up to 12 mSv/y. As for adults, the effective dose exceeds this value in 92% of Cm-V waters.

**Table 3 Average effective doses for adults and infants for Cambrian V group waters and percentage contributions of the two radium isotopes (Forte et al., 2010)**

| Nuclide | Adults | Infants |
|---|---|---|
| | Average effective doses (mSv/y) | |
| $^{228}Ra + ^{226}Ra$ | 0.3 ± 0.2 | 3.6 ±1.9 |
| **Nuclide** | **Percentage of the total dose** | |
| $^{228}Ra$ | 74% | 88 % |
| $^{226}Ra$ | 26% | 12% |

As for non Cm-V waters (Forte et al, 2010), available data are very scarce; in any case, effective doses for infants always exceed 0.1 mSv/y, whereas those for adults, in 79% of the cases.

**Figure 1 Committed effective doses for infants from Cm-V group waters**




Some conclusions can be drawn from this study.

Given its high radio-toxicity, knowledge of the activity concentrations of $^{228}Ra$ should be improved in drinking water worldwide, and particular attention should be given to doses for lower age classes and screening values when radium isotopes are the prevailing radionuclides in water. Concerning screening values, the values of 0.5 Bq $l^{-1}$ for alpha emitters and 1 Bq $l^{-1}$ for beta emitters, suggested by the *WHO Guidelines for drinking water* (WHO, 2004), may be not precautionary. Indeed, in case of adult population an activity concentration of 0.5 Bq $l^{-1}$ of the alpha emitter $^{226}Ra$ alone leads to 0.1 mSv/y TID, whereas an activity concentration of 1 Bq $l^{-1}$ of the beta emitter $^{228}Ra$ leads to much higher dose rates

(0.5 mSv/y). In case of infants the situation would be much more critical because 0.5 Bq $l^{-1}$ of the alpha emitter $^{226}$Ra alone leads to about 0.6 mSv/y and 1 Bq $l^{-1}$ of beta emitter $^{228}$Ra leads to much higher dose rates (7.5 mSv/y).

Moreover, radium isotopes are also significant for doses to adolescents. For a detailed discussion see (Forte et al., 2010).

In any case, attention should be paid to doses from drinking water to infants and small children, as it is easily shown by calculating the derived reference levels starting from the parametric value for TID of 0.1 mSv/y (EC, 1998), and using the WHO consumption assumptions for different age classes (WHO, 2004). Derived reference levels for infants (< 1 year) and small children (1-2 year age group) are the lowest ones for almost all radionuclides, notwithstanding lower annual intakes by infants and children (Risica and Grande, 2000).

*WHO Guidelines for drinking water* accounted for adult exposure only. The Council Directive 98/83/EC (EC, 1998) requires - without any other specification - that a parametric value of 0.1 mSv/y for the Total Indicative Dose be applied. It is therefore reasonable to assume that it is applicable to all age classes of the population, but new specifications are expected. No specific recommendation or regulation on the use of water by lower age classes has ever been issued at the international level, whereas at the national level two examples can be reported. In Italy some recommendations for mineral and spa water used by infants were suggested by our Institute (Nuccetelli et al., 2004) and adopted by the Ministry of Health. In Germany a regulation concerning $^{226}$Ra and $^{228}$Ra in drinking and mineral water was issued in 2006 (BGBl, 2006).

## 4.4 $^{220}$Rn (radon, Rn) *versus* $^{222}$Rn (thoron, Tn)

It is well known that $^{222}$Rn being a noble gas, the significant quantity for the dose is the indoor concentration of $^{222}$Rn decay products. The same holds for $^{220}$Rn.

Population exposure to indoor concentrations of $^{220}$Rn and its decay products may be non-negligible in buildings where soil or building material, or both, are rich in $^{232}$Th. The same holds for occupational exposure in industries where Th-rich sands/ores are handled or Th welding rods are used (but occupational exposure is not discussed here). For example in a survey on 205 dwellings in Ireland (McLaughlin, 2010), in 14 out of the 205 dwellings the estimated annual dose from $^{220}$Rn decay products exceeded that from $^{222}$Rn. Even if the 205 dwellings investigated cannot be considered to be a representative sample of the national housing stock, this is a significant result.

Table 4 reports main nuclear data of $^{222}$Rn and $^{220}$Rn and decay products (DPs).

**Table 4 $^{222}$Rn and $^{220}$Rn and their main decay products nuclear data: recommended by (DDEP, 2010)**

| Nuclide | Half-life | Decay | Energy (MeV) | Nuclide | Half-life | Decay | Energy (MeV) |
|---|---|---|---|---|---|---|---|
| $^{222}$Rn | 3.82 d | α | 5.5 | $^{220}$Rn | 55.8 s | α | 6.3 |
| $^{218}$Po | 3.09 min | α | 6.0 | $^{216}$Po | 0.15 s | α | 6.8 |
| $^{214}$Pb | 26.8 min | β,γ | | $^{212}$Pb | 10.6 h | β,γ | |
| $^{214}$Bi | 19.9 min | β,γ | | $^{212}$Bi | 60.5 min | β,γ | |
| $^{214}$Po | 162 µs | α | 7.7 | $^{212}$Po | 0.3 µs | α | 8.8 |
| $^{210}$Pb | 22.2 y | β,γ | | $^{208}$Pb | stable | | |

The much shorter half-life of $^{220}$Rn with respect to $^{222}$Rn means that $^{220}$Rn is much less capable of escaping from the site where it is formed, generally rendering its presence in indoor air of low significance as regards the health effects. However, $^{220}$Rn decay products have a half-life of some hours and are generally quite homogeneously mixed in an indoor environment.

The first decay products of both $^{222}$Rn and $^{220}$Rn have short half-lives, and some of them are high-energy alpha emitters. However, $^{220}$Rn decay product $^{212}$Pb presents a relatively long half-life (10 h) which allows it, once inhaled, to be more easily absorbed by the lungs, and to irradiate other body organs, in comparison to $^{222}$Rn decay products (Kendall and Phipps, 2007).

$^{220}$Rn concentration cannot be predicted from $^{222}$Rn measurements, *vice versa* it can be a source of error in residential radon studies. Indeed, unless the radon detector is well designed to avoid $^{220}$Rn entry, the $^{222}$Rn detector may result in incorrect estimates (Tokonami, 2010). This is the reason why UNSCEAR recommends that future measurements studies should consider the contribution of both $^{222}$Rn and $^{220}$Rn to exposure (UNSCEAR, 2006).

Measurement techniques for $^{220}$Rn and its decay products are less advanced than those for $^{222}$Rn. Unlike for $^{222}$Rn decay products, accurate passive dosimeters for $^{220}$Rn decay products have been mostly developed in the last years. Moreover, up to now few high quality reference chambers have been set up, and they still show significant discrepancies (Sorimachi et al., 2010). It was only in 2008/2009 that the first international intercomparison of detectors was organized by the *National Institute of Radiological Sciences* (NIRS) of Japan: of the 9 participants for $^{220}$Rn measurements, 3 were from EU, and only 6 sent back results (Janik et al., 2010). Lastly, only very recently has a primary standard of $^{220}$Rn been set up at the *Physikalisch-Technische Bundesanstalt* (PTB) of Germany (Röttger et al., 2010).

As far as health risk assessment is concerned, dosimetric models are available for both $^{220}$Rn and $^{222}$Rn; epidemiological data only for $^{222}$Rn.

As for $^{220}$Rn dose coefficient, the latest ICRP dosimetric approach was issued in 1987 (ICRP, 1987), and assumed dose coefficients based on old dosimetric models (available in 1983). In

1998 a *comparative* dosimetric approach was proposed (Nuccetelli and Bochicchio, 1998), a choice that was supported by dosimetric calculations based on the latest ICRP human respiratory tract model (Marsh and Birchall, 1999).

UNSCEAR, in its 2000 Report, using an analogous *comparative* dosimetric approach, assessed an effective dose of 40 nSv per unit exposure (in Bq h $m^{-3}$) to an Equilibrium Equivalent Concentration (EEC)[1] of $^{220}$Rn (UNSCEAR, 2000).

In 2006, UNSCEAR confirmed the 2000 estimate (UNSCEAR, 2006), but in 2007 two papers highlighted differences with the USCEAR estimate.

Ishikawa et al. (Ishikawa et al. 2007) assessed the dose coefficient in dwellings, obtaining 7 nSv/(Bq h $m^{-3}$) with a comparative approach, and 116 nSv/(Bq h $m^{-3}$) with a dosimetric evaluation.

Kendall and Phipps (Kendall and Phipps, 2007) calculated the dose coefficient of $^{220}$Rn, in terms of Sv/Bq, showing that this coefficient is probably 2 to 3 times higher than the UNSCEAR estimate. They also studied the dose coefficient for children, which was rather larger than for adults, but counterbalanced by children's lower breathing rate.

In conclusion, more studies and research activities are needed in this field, as stressed in several lectures given at the latest workshop devoted to $^{220}$Rn issues (Thoron 2010, Workshop & Intercomparison, NIRS, Chiba, Japan); the main papers presented there are available in a special issue of an international journal (International Workshop, 2010).

As regards $^{220}$Rn regulation, Title VII of EURATOM 96/29 Directive (EC, 1996) suggested general criteria to restrict exposure of workers not only to $^{222}$Rn but also to $^{220}$Rn, but proposed no limit or recommended values and no further decision was taken in the new draft EURATOM Directive (EC, 2010).

In its draft Basic Safety Standards, IAEA does not suggest any level of regulation of $^{220}$Rn indoors.

Lastly, as far as we know, no European country has so far established clear-cut limitations of $^{220}$Rn in workplaces or indoors. Probably monitoring and dosimetric difficulties should be solved first.

It is interesting to note that UNSCEAR (UNSCEAR, 2006) recognised that $^{220}$Rn was neglected in the past: "*In the past, exposures to Tn and its decay products were often ignored ... it has become increasingly clear that the exposure to Tn and its decay products cannot be ignored in some environments (both workplaces and residential) as it contributes to the risks otherwise assigned solely to Rn and its decay products .... data collected for the present study indicate that the levels of Tn (and hence doses from exposure to Tn and its decay products) are highly variable and that Tn may provide a larger contribution to natural background dose than previously thought. Doses from Rn and Tn represent approximately half of the estimated dose from exposure to all natural sources of ionizing radiation*".

## 4.5 Conclusions

The lecture highlighted some gaps of knowledge on $^{232}$Th and its decay products, which shows that research activities in this area should be further encouraged.

---

[1] *Equilibrium Equivalent Concentration* is a special unit, used for $^{222}$Rn and $^{220}$Rn decay products, which is defined as the equivalent concentration of the decay products in equilibrium with the parent gas that yields the same potential alpha energy per unit volume as the existing mixture.
EEC($^{220}$Rn) = 0.91 ($^{212}$Pb) + 0.087($^{212}$Bi), where $^{212}$Pb, $^{212}$Bi and EEC are activity concentrations in Bq/$m^3$.

In particular, activity concentrations of $^{232}$Th and its decay products in the diet and in the indoor/outdoor environment should be investigated. This requires an interdisciplinary effort, because some of the radionuclides in the $^{232}$Th chain are only measurable with radiochemical and/or chemical (e.g. ICPMS) techniques.

Serious effort is also needed into improving both $^{220}$Rn measuring techniques - i.e., new detection techniques, traceable standards, reference materials and organisation of intercomparison runs - and $^{220}$Rn dosimetry, in order to get an international agreement on dose coefficients. This will further help solve the already cited emerging problem of $^{220}$Rn contribution to $^{222}$Rn measurements in epidemiological studies.

Moreover, recent studies have stressed that $^{220}$Rn-prone areas are much more numerous than previously thought, therefore systematic surveys are needed to identify these areas worldwide (Akiba et al, 2010).

In the authors' opinion some policy implications originate from the presented analysis.

In assessing doses, attention should be paid to lower age classes and screening levels of total alpha and beta activity concentration in drinking water. The latter should be used taking into account that in some situations they can underestimate actual effective doses, as highlighted in the case of $^{228}$Ra in Estonian Cm-V waters. Lastly, it is the authors' opinion that time is ripe to introduce new requirements regarding the presence of radioactivity in mineral and spa water.

As regards $^{220}$Rn, it seems that time is not ripe to launch an initiative to limit its concentration: there are still severe gaps of knowledge in both measurements techniques and dosimetry.

On the other hand, the authors are convinced that environmental monitoring, as indicated by the European Recommendation 2000 (EC, 2000), should be extended to major natural radionuclides in order to draw a natural background scenario and highlight critical exposures.

## 4.6 Acknowledgements

The authors are very grateful to Monica Brocco (ISS) for the linguistic revision of the manuscript.

## 4.7 References

Akiba S., Tokonami S., Bochicchio F., McLaughlin J., Tommasino L., and Harley N. *Thoron: its metrology, health effects and implications for radon epidemiology: a summary of roundtable discussions*. Radiat. Prot. Dosim. 141(4), 1-5.

Bundesgesetzblatt (BGBl)( 2006). *Mineral- und Tafelwasser-Verordnung*, I. Nr.56 vom 11. Dezember 2006.

Decay Data Evaluation Project (DDEP) (2010) (http://www.nucleide.org/DDEP.htm).

EC (1996). *COUNCIL DIRECTIVE 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of the workers and the general public against the dangers arising from ionizing radiation.* Official Journal of the European Communities L 159, 29.6.96).

Eisenbud M. (1987). *Environmental Radioactivity, from Natural, Industrial and Military sources*. Academic Press Inc. (London) UK.

European Commission (EC) (1998): *COUNCIL DIRECTIVE 98/83/EC of 3 November 1998 on the quality of water intended for human consumption*. Official Journal of the European Communities L330/32, 5.12.98.

European Commission (EC) (2000). *Commission Recommendation of 8 June 2000 on the application of Article 36 of the Euratom Treaty concerning the monitoring of the levels of radioactivity in the environment for the purpose of assessing the exposure of the population as a whole.* Official Journal of the European Communities L 191/37, 27.7.2000.

European Commission (EC) (2010). *Draft Euratom Basic Safety Standards Directive* http://ec.europa.eu/energy/nuclear/radiation_protection/doc/art31/2010_02_24_draft_euratom_basic_safety_standards_directive.pdf.

Forte M., Bagnato L., Caldognetto E., Risica S., Trotti F. and Rusconi R. (2010). *Radium isotopes in Estonian groundwater: measurements, analytical correlations, population dose*, J. Radiol. Prot. 30, 761 - 780.

International Commission on Radiological Protection (ICRP), (1987). *Publication 50. Lung cancer risk from Indoor Exposures to Radon Daughters*. Ann. ICRP 17(1), Oxford, Pergamon.

International Commission on Radiological Protection (ICRP), (1996). *Publication 72. Age-dependent Doses to Members of the Public from Intake of Radionuclides: Part 5 Compilation of Ingestion and Inhalation Dose Coefficients*. Ann. ICRP 26(1).

*International Workshop on Environmental Thoron and Related Issues*: special issue of Radiat. Prot. Dosim. November 2010; vol. 141, no. 4.

Ishikawa T., Tokonami S., and Nemeth C. (2007). *Calculation of dose conversion factors for thoron decay products*. J. Radiol. Prot. 27,447-456.

Janik M., Tokonami S., Kranrod C., Sorimachi A., Ishikawa T. and Hassan N.M. (2010) *International intercomparisons of integrating radon/thoron detectors with the NIRS radon/thoron chambers*. Radiat. Prot. Dosim. 141(4),436-439.

Kendall G.M. and Phipps A.W.(2007). *Effective and organ doses from thoron decay products at different ages*. J. Radiol. Prot. 27, 427-435.

Marsh J.W. and Birchall A. (1999) *Letter to the editor*, Radiation Protection Dosimetry, 81(4) 311-312.

McLaughlin J. (2010). *An overview of thoron and its progeny in the indoor environment*. Radiat. Prot. Dosim. 141(4), 316-321.

Nuccetelli, C. and Bolzan, C., 2001. *In situ gamma spectroscopy to characterize building materials as radon and thoron sources*. Sci. Total Environ. 272, 355–360.

Nuccetelli C. and Bochicchio F. (1998). *The thoron issue: monitoring activities, measuring techniques and dose conversion factors*. Radiat. Prot. Dosim. 78(1), 59-61.

Nuccetelli C. and Risica S. (2008). *Thorium series radionuclides in the environment: Measurement, dose assessment and regulation.* Appl. Radiat. Isot. 66(11), 1657-60.

Nuccetelli C., Bochicchio F., Ruocco G., (2004*). Natural radioactivity in mineral and spa waters: the current regulatory approach in Italy*. In: Proceedings of the 11th International Congress of the International Radiation Protection Association, Madrid, Spain, 23-28 May, 2004. (CD rom).

Risica S., Bolzan C., Nuccetelli C. (2001). *Radioactivity in building materials: room model analysis and experimental methods*. Sci. Total Environ. 272, 19-126.

Risica, S. and Grande, S. (2000). *Council Directive 98/83/EC on the quality of water intended for human consumption: calculation of derived activity concentrations*. Rapporti ISTISAN 00/16, p.47, available at: http://www.iss.it/binary/publ/publi/0016.1109850012.pdf.

Röttger, A., Honig A., Dersch R., Ott O., Arnold D. (2010). *A primary standard for activity concentration of $^{220}$Rn (thoron) in air*. Appl. Radiat. Isot. 68, 1292-1296.

Sorimachi A., Ishikawa T., Janik M. and Tokonami S. (2010). *Quality assurance and quality control for thoron measurement at NIRS*. Radiat. Prot. Dosim. 141(4), 367-370.

Tokonami S. (2010). *Why is $^{220}$Rn (Thoron) measurement important?* Radiat. Prot. Dosim. 141(4), 335-339.

Trevisi R., D'Alessandro M., Nuccetelli C., Risica S.(2008). *Radioactivity in Building Materials: a first Overview of the European Scenario*, Proceedings of the IRPA 12 Conference, Buenos Aires October 20 – 24, 2008. STI/PUB/1460 (ISBN 978-92-0-105410-4). TS III.4.4, 3464.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2000). *Sources and Effects of Ionizing Radiation,* UNSCEAR Report 2000. United Nations, New York, 2000.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2009). *Effects of Ionizing Radiation,* UNSCEAR 2006 Report, volume II Annex E. United Nations, New York, 2009.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2010). *Sources and Effects of Ionizing Radiation.* UNSCEAR 2008 Report, volume I, Annex B. United Nations, New York, 2010.

World Health Organization (WHO) (2004). *Guidelines for Drinking-water Quality*. Third edition, Volume 1 Recommendations, World Health Organization Geneva, 2004.

# 5 THYROID CANCER AFTER THE CHERNOBYL ACCIDENT - LESSONS LEARNED, AN UPDATE

**Dillwyn Williams**

***Strangeways Laboratory, University of Cambridge,***
***2 Worts Causeway, Cambridge, CB1 8RN, UK***

## 5.1 Introduction

The accident at Chernobyl on April 26th 1986 remains an iconic event in the minds of the population of Europe. It led to the exposure of millions of people to radiation from fallout, the major constituent of which, ignoring the inert gas Xenon 133, was radioactive isotopes of iodine. About $2x10^{18}$ Bq of $^{131}I$ was released, together with about $1x\ 10^{18}$ Bq of $^{132}Te$, rapidly decaying to $^{132}I$. Large amounts of other isotopes of iodine with extremely short half-lives were also released. About 4 years after the accident an increase in the incidence of thyroid carcinoma in children was noted in both main hospitals caring for the population of the most exposed areas, in Minsk and Kiev. To date, thyroid cancer has been the main direct consequence of exposure to fallout in the population in Belarus, northern Ukraine, and the oblasts of the Russian Federation closest to Chernobyl.

While this paper is specifically concerned with thyroid cancer in those exposed to fallout it is worth noting that a rise in breast cancer incidence in a highly exposed area has been attributed to radiation (Pukkala et al 2006). Many of the cancer and non-cancer consequences of exposure to atomic bomb radiation were not observed until decades after the event, so that other non-thyroid effects may occur in the future in those exposed to fallout. A range of non-thyroid consequences, including haematological malignancies and cataract, have been observed in the liquidators (emergency workers), particularly those working at the reactor site shortly after the accident. 28 of these died of acute radiation sickness in the few weeks following the accident.

The exposure of the general population was at first almost entirely to internal radiation from ingested or inhaled isotopes from fallout. The exposure from isotopes of iodine declined rapidly with time, due to the short half-life (8.1 days) of Iodine 131, and the biological half-life of iodine stored in the thyroid gland. Over time a contribution from radiation from ground deposition and ingestion of isotopes other than iodine, particularly Cesium 134 and 137 outweighed that from any residual Iodine 131, but contributed only a small fraction of the accumulated dose to the thyroid. This pattern of exposure is similar to that which would be expected if another nuclear accident with a major release of isotopes to the environment were to occur.

The exposure to the general population after Chernobyl is quite different from that which occurred after the atomic bombs. In Japan the exposure was external rather than internal, the radiation was from gamma rays and neutrons rather than beta and gamma rays, the tissue distribution was uniform rather than very variable, and the dose rate was extremely high rather than low. It is clearly important that we learn all we can of the consequences of exposure to the Chernobyl accident.

## 5.2 Size of the thyroid cancer increase

The position in the first 20 years after the accident was summarised in the findings presented in the WHO/IAEA report (WHO 2006). This attributed 4000 excess cancers to exposure to Chernobyl, although it was not made clear in the press release that this referred only to the most exposed areas. There are several uncertainties in establishing the size of the increase, either as an absolute number or as an increase in incidence. The need to define the area studied has been mentioned, comparing the incidence in exposed and unexposed areas may be complicated by ethnic and environmental factors, and by the difficulty in defining unexposed areas, when most of Europe was exposed to low level fallout deposition. Perhaps the biggest problem is the increased ascertainment in areas designated as contaminated, where the general public and health professionals will be aware of the increased risks, and are more likely to undergo careful examination or participate in screening programmes. Observed increases in incidence must also be considered in the light of world-wide increases in the incidence of papillary carcinoma of the thyroid, in part at least due to increasing use of techniques like ultrasound and fine needle aspiration. A continuing excess incidence of thyroid carcinoma has been reported from Belarus (Demidchik, 2005, Bespalchuk et al 2009), and in Ukraine (Fuzik et al 2010). In the latter paper truncated age standardised rates ($/10^5$) for thyroid cancer in the high-exposure areas reached 20.68 in females aged 40-59 in 2000-2004. The rates for females aged 20 and over in the high-exposure areas were 2.37 to 2.52 times higher in 2005 to 2008 than in 1989. In the low exposure areas the comparable figures were 1.51 to 2.27. The rates were consistently higher in the high compared to the low exposure areas, but as the authors comment ecological bias could be relevant. The attributable fraction for thyroid carcinoma among those who were children or adults at the time of the accident has been estimated as about 60% for Belarus, and 30% for Ukraine (Jacob et al 2006a). The same authors also found that the baseline incidence was higher in the more exposed regions, presumably due to greater ascertainment. The importance of increased ascertainment is shown by the increase in the proportion of small thyroid carcinomas (less than 2cm in diameter at surgery) between 1990-95 and 1996-2001 (Tronko et al 2005) (Fig 1). There was little change in 2002, suggesting that the increased awareness and greater screening took place in the early years after the role of radiation in the increase was established. Providing an accurate estimate of the number of thyroid carcinomas attributable to the Chernobyl accident to date is difficult because of the uncertainties involved, and the variables which will be discussed in relation to estimates of the risk per Gray. These also influence predictions of the future, the numbers expected up to 2056 have been estimated as 15,700 (Cardis et al, 2006) and 92,627 (Malko, quoted in Yablokov, 2009).

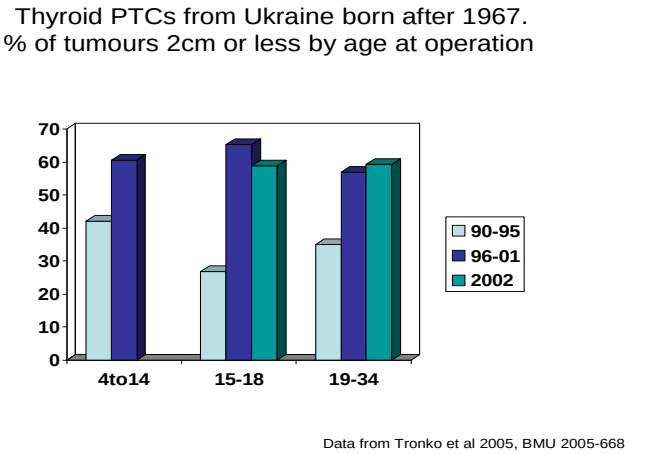



**Figure 1 Increasing proportion of smaller tumours with increasing latency**

## 5.3 Thyroid Carcinoma risk

Estimates of the risk/Gy also vary greatly. An excess relative risk (ERR) of 48.7/Gy was reported by studies of exposed areas in Russia, (Kopecky et al, 2006). A different group, also studying cases from Bryansk Oblast found ERRs varying from 28.8 to 177.4/Gy in different groups studied (Ivanov 2006). Studies of selected settlements in Ukraine and Belarus reported an ERR of 18.9 (Jacob et al 2006b), while a population based case control study in Belarus and the Russian Federation found an odds ratio at 1Gy of 5.5 to 8.4 (Cardis et al 2005). An Ukranian study reported an ERR of 8.0/Gy (Likhtarov et al 2006), while a study based on a screened Ukranian population found an ERR/Gy of 5.25 (Tronko et al 2006). A similar recently reported screening study in Belarus found an excess odds ratio/Gy of 2.15 (Zablotska et al 2010). These studies differ in a number of ways, the area studied, the level of exposure, the time over which the cases were collected, the level of confirmation of the diagnosis and the type of study (ecological or case control). In one study the cases selected were under 15 at exposure, in the remainder they were under 19. The results in general had wide confidence limits. Ron concluded that the magnitude and patterns of thyroid cancer risk reported after Chernobyl are generally consistent with those reported following external exposure (Ron, 2007).

Reporting an overall figure for the risk of developing thyroid carcinoma after exposure to radiation conceals the effects of a number of variables. The major one is age at exposure. There is no doubt that young children exposed to external radiation are at a greater risk of developing thyroid cancer than older children, and that adults have little or no risk (Ron et al, 1995). There is also no doubt that in the population exposed to fallout after Chernobyl the risk of developing thyroid cancer was greatest in young children, falling rapidly with increasing age at exposure (Williams 1996). The relationship with age at exposure is shown in Fig 2, where the numbers of thyroid carcinomas occurring in 2 oblasts of Belarus up to 2002 are shown for those under 19 at the accident by date of birth. Gomel was the most exposed oblast of Belarus, and Vitebsk was the least, receiving about 1% of the level of fallout of Gomel. Gomel has a slightly larger population. The high incidence in the youngest at exposure is in part due to the increased intake and uptake of radioactive iodine by the thyroid. There is dispute as to the change in the risk/Gy with age, but the accuracy of dose reconstruction in children must also be considered.

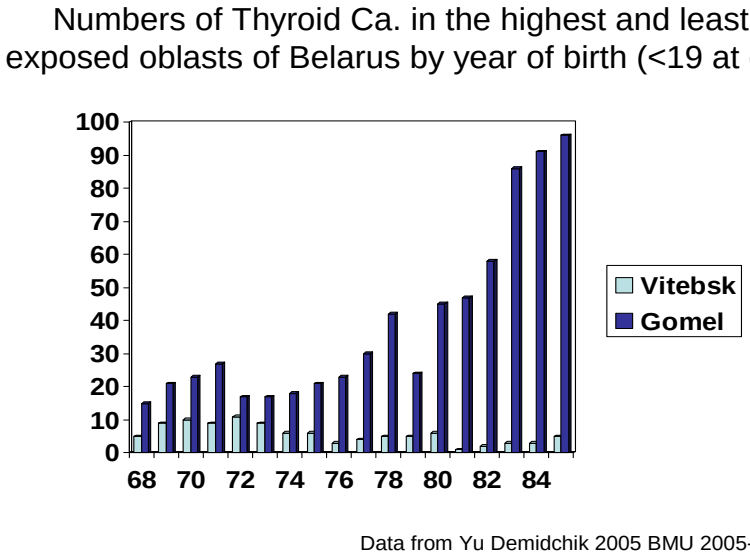



**Figure 2 Influence of age at exposure on thyroid carcinoma risk**

Those exposed at a young age carry the increased risk into adulthood (Fig3), and a recent study in Ukraine has shown an increased incidence in the high compared to the low exposure areas, continuing up to the last period studied, 2004 to 2008 (Fuzik et al, 2010). The increase was seen in this period in all age groups except for those aged below 20, where virtually all the cases would have been born after the accident, and was more marked in those aged 20-39 at operation than older groups. The authors suggest that there may be an increased incidence in those exposed as adults at all ages, and also that there may be a longer latent period in those exposed at older ages. These are both important points, but the study seems to have a major problem with ascertainment; the incidence rate for those born after the accident in the high exposure regions and aged 15-19 at diagnosis is nearly double that in the low exposure regions. Many studies have now shown the importance of a young age at exposure to the risk of thyroid cancer, most agree that the risk to adults is not yet confirmed, but if present is likely to be small.

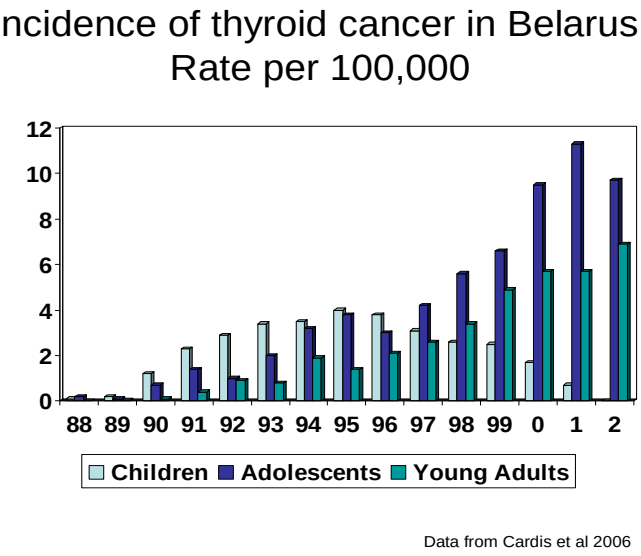



**Figure 3 Peak incidence of thyroid carcinoma passing from children to adolescents to adults as the at risk population ages.**

Another major variable affecting risk is the level of dietary iodide. Administration of stable iodide shortly before or within a few hours after exposure can of course block the uptake of radioactive iodine, but few of those exposed after Chernobyl received stable iodine within those time constraints. The areas around Chernobyl are variably iodine deficient, in addition long term administration of low dose stable iodine was given to some after the accident. The role of iodine deficiency was studied in the Bryansk oblast of Russia, and the ERR for thyroid cancer in areas with severe iodine deficiency was found to be approximately twice that in areas with normal iodide levels (Shaktarin et al 2003). Another study found a higher ratio, approximately three fold, and also showed that supplementary iodide intake lowered the risk in both the higher and lower iodide levels (Cardis et al 2005). These results are important, but should not be surprising. Thyroid growth is known to be important to thyroid carcinogenesis (Williams, 1992), radiation can increase TSH levels, and raising dietary iodide can reduce them. Abolishing thyroid growth by hypophysectomy or high levels of thyroxin prevents radiation carcinogenesis in the animal thyroid. It is important for many reasons to use iodide supplementation in areas of iodine deficiency, but, as was suggested to the IAEA shortly after the Chernobyl accident, the use of long-term dietary iodide administration in populations exposed to fallout containing radioactive iodine should be considered.

Other factors relevant to the risk of developing thyroid carcinoma after radiation exposure include genetic susceptibility. Polymorphic variants of DNA repair genes such as XRCC and ATM have been associated with an increased risk or radiation induced thyroid cancer, both after Chernobyl and after exposure to nuclear tests, but they have also been linked to sporadic thyroid cancers (Adjadj et al, 2009: Akulevich et al 2009: Bastos et al, 2009).

## 5.4 Changes with latency

Studies of the consequences of the Chernobyl accident allow studies of the changes with latency, as there have been such a large number of cases of one type of tumour where it can be presumed that the mutation initiating the carcinogenic process occurred within a few days or weeks of April 26$^{th}$ 1986. With increasing latency the papillary carcinomas (PTCs) that form the great majority of the radiation induced cases have become smaller, and clinically less aggressive (Demidchik 2006). Pathology studies have shown that the PTCs are more mature, with solid type tumours predominating in the early cases, and classic type PTCs in the later cases. No definite rise in the incidence of follicular carcinomas has yet been demonstrated. In keeping with the changes in morphology the proportion of tumours showing direct invasion fell, and these changes were shown to be related to latency rather than age at operation (Williams et al, 2004). Molecular findings in the PTCs have also changed with latency, initial studies found that almost all showed a RET-PTC rearrangement, dominantly RET-PTC3. With increasing latency the proportion of cases with RET-PTC rearrangements has fallen, and an increasing proportion of these have been RET-PTC1 (Rabes et al, 2000). A small proportion of the cases have shown BRAF point mutations (Lima et al 2004).

## 5.5 Molecular findings and radiation

The great majority of sporadic PTCs show either a RET or a BRAF mutation, only rarely are the two oncogenes found to be mutated in the same tumour(Soares 2003). The proportion varies, in most European and American studies they are often fairly equal in distribution, with very few cases lacking either. PTCs in the Chernobyl exposed population have shown only a small proportion with BRAF mutations and often a significant number in which neither have been found.

The RET oncogene is activated by rearrangement, bringing the tyrosine kinase part of the gene under the control of an active promoter, at least 15 variants have been described. In sporadic tumours the variants 1 and 3 are the most common, with rare RET-PTC 2 tumours found. Most of the other variants have been found in radiation related tumours following Chernobyl. The BRAF oncogene is activated by point mutation, very nearly always a V600E mutation. Radiation is known to be effective at inducing double strand breaks, the precursor of rearrangements, and it has been suggested that an increase in oncogenes activated by rearrangement is typical of radiation induced tumours (Williams, 2009). This is supported by the finding of rearrangements in BRAF in Chernobyl related tumours (Ciampi et al, 2005). One of the problems in latency related studies is that latency correlates with increasing age, and it is important to separate the two. It has been suggested that the low frequency of BRAF mutations in Chernobyl related tumours is due to the young age of those studied; BRAF mutation is known to be less common in childhood than adult thyroid cancer. This seems not to be the explanation, BRAF mutations have been found to be under-represented in external radiation induced thyroid carcinomas (Collins et al 2006), and a recent study of PTCs in the atomic bomb exposed population has clearly shown that in the population exposed to less than 70mGy, in whom the attributable fraction would be expected to be low, BRAF mutations are common and RET-PTC rearrangements uncommon. In contrast, in those exposed to 0.5

to 3Gy most mutations identified were RET-PTC rearrangements, and BRAF point mutations were uncommon (Hamatani et al 2009). As in the Chernobyl population tumours lacking identified RET or BRAF mutations were more common in the high dose population; these should be studied to see if further oncogene rearrangements are present.

## 5.6 Lessons drawn from the Chernobyl accident

The clear evidence from all studies of the strong correlation between a young age at exposure and the risk of developing thyroid cancer poses a problem for action in the event of another similar accident. The risk is so much higher in the youngest children that it seems advisable to give priority to this group. A pooled analysis of 7 studies of radiation induced thyroid cancer found the risk/Gy 5 fold higher in those under 4 at exposure when compared to those aged 10-14 (Ron et al, 1995). A study of thyroid carcinomas as second tumours in children receiving radiotherapy for the first tumour found a ten fold difference in ERR/Gy between those treated under 1 year of age, and those aged 15-20; the decrease with increasing age was consistent and linear (Ronckers et al, 2006). The Chernobyl data suggest a similar ratio, although possibly with the first 3 years of life being particularly sensitive. The practicality of dealing with the immediate consequences of a nuclear accident are such that rather than setting a specific age it would be better to deal with categories such as preschool infants, schoolchildren, high/secondary school children and adults. A study devoted to establishing the definitive relationship between age at exposure and risk of developing thyroid cancer after Chernobyl is needed, to see whether pre-school children should be recognised as those at the highest risk, and given special priority in plans to respond to a nuclear accident.

The evidence from Chernobyl studies of the major influence of dietary iodine status on the risk of developing thyroid carcinoma after fallout exposure is likely to be relevant to differences in risks reported by different studies, for example the very low risk reported after exposure to fallout from nuclear bomb testing in the United States, a country with a high stable iodine intake (Gilbert et al 2010). Stable iodine administration shortly before or after exposure to fallout is important to reduce uptake of radioactive iodine, but long-term dietary supplementation with stable iodine is also relevant, particularly in iodine deficient areas.

These two lessons from studies of those exposed to the Chernobyl accident combine when considering how to express the risk of developing thyroid carcinoma after exposure to fallout. The ERR/Gy will be affected by both, and it will be necessary to specify the group referred to, for example children under 3 from an iodine deficient area, rather than imply that a single ERR is generally applicable. It should also be remembered that because a Gy is a measure of energy absorbed per unit volume, the risk to an individual depends on the volume of the gland, and the thyroid is larger in iodine deficiency than in areas with normal dietary iodine.

One of the most important lessons from the study of the thyroid carcinomas that have occurred as a result of exposure to fallout from the Chernobyl accident is that the morphological, clinical and molecular findings all change with increasing latency. These changes are likely to continue, and the future may see increases in follicular carcinomas of the thyroid, and possibly of other thyroid malignancies. The consequences for the development of malignant or non-neoplastic disease in other organs in the future strengthen the case for long-term studies of this unique event.

## 5.7 References

Adjadj E, Schlumberger M, de Vathaire F. Germline polymorphisms and susceptibility to differentiated thyroid cancer, Lancet Oncol 2009, 19;181-190.

Akulevich NM, Saenko VA, Rogonouvich TI et al, Polymorphisms of DNA damage response genes in radiation related and sporadic papillary carcinoma. Endocr related Cancer, 2009; 16:491-503.

Bastos HN, Antao MR, Silva SN et al, Associations of polymorphisms of genes of the homologous recombination DNA repair pathway and thyroid cancer risk. Thyroid 2009, 19:1067-1075.

Bespalchuk PI, Demidchik,YE, Demidchik EP et al, in Radiation Health Risk Sciences, ed Nakashima M et al, Springer Tokyo, 2009.

Cardis E, Kesminiene A, Ivanov V, et al.: Risk of thyroid carcinoma after exposure to $^{131}$I in childhood. J Nat Canc Inst; 2005 ; 97:1–9.

Cardis E, Krewski D, Boniol M et al. Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. Int J Cancer 2006; 119: 1224-35.

Ciampi R, Knauf RA, Kerler R, et al.: Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J Clin Invest 2005;115:94–101.

Collins BJ, Schneider AB, Prinz RA, et al.: Low frequency of BRAF mutations in adult patients with papillary thyroid cancers following childhood radiation exposure. Thyroid 2006;16: 61–66.

Demidchik Y, Thyroid cancer of Belarussians having been exposed as children or adolescents as a result of the Chernobyl accident. Report of the German Federal Office for Radiation Protection, 2005. BMU-2005-668, appendix 8, 1-20.

Demidchik Y E, Demidchik E P, Reiners C et al. Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. Ann Surg 2006; 243: 525-32.

Fuzik M, Prysyazhnyuk A, Shibata Y et al, Thyroid carcinoma incidence: trends with reference to the Chernobyl accident. Radiat Environ Biophys 2010, published online 10.11.2010.

Gilbert ES, Huang L, Bouville A et al. Thyroid cancer rates and $^{131}$I doses from Nevada atmospheric nuclear bomb tests: an update. Radiat Res, 2010; 173:659-664.

Hamatani K, Eguchi H, Ito R et al RET/PTC rearrangements preferentially occurred in papillary thyroid carcinoma among atomic bomb survivors exposed to high radiation dose. Cancer Res 2008; 68:7176-82.

Heidenreich WF, Bogdanova TI, et al. Time trends of thyroid cancer incidence in Ukraine after the Chernobyl accident. J Radiol Protection 2004; 283-293.

Jacob P, Bogdanova TI, Buglova E et al, Thyroid cancer among Ukrainians and Belarussians. J Radiol Protection 2006a; 26:51-67.

Jacob P, Bogdanova TI, Buglova E et al, Thyroid carcinoma risk in areas of Ukraine and Belarus affected by the accident. Radiat Res, 2006b; 165: 1-8.

Ivanov VK, Gorski AI, Tsyb AF et al, Radiation-epidemiological studies of thyroid cancer incidence. Radiat Environ Biophys, 2006; 45: 9-16.

Kopecky KG, Stepanenko V, Rivkind N et al Childhood thyroid cancer, radiation dose from Chernobyl. Radiat Res, 2006; 166: 367-74.

Lima J, Trovisco V, Soares P, et al.: BRAF mutations are not a major event in post-Chernobyl childhood thyroid carcinomas. J Clin Endocrinol Metab 2004;89:4267–4271.

Likhtarov I, Kovgan L, Vavilov S et al. Post-Chernobyl thyroid cancers in Ukraine. Radiat Res, 2006; 166:375-386.

Pukkala E, Kesmininene A, Poliakov S et al. Breast cancer in Belarus and Ukraine after the Chernobyl accident. Int J Cancer 2006; 119:651-8.

Rabes HM, Demidchik EP, Siderow JD, et al.: Pattern of radiation induced RET and NTRK1 rearrangements in 191 post Chernobyl papillary carcinomas: Biologic, phenotypic and clinical implications. Clin Cancer Res 2000; 6:1093–1103.

Ron E, Lubin JH, Shore RE, et al.: Thyroid cancer after exposure to external radiation, a pooled analysis of 7 studies. Radiat Res 1995;141:259–277.

Ron E Thyroid cancer incidence among people living in areas contaminated by radiation from the Chernobyl accident. Health Phys 2007; 93:502-11.

Ronckers CM, Sigurdson AG, Stovall M et al: Thyroid cancer in childhood cancer survivors. Radiat Res 2006; 166: 618-28.

Shaktarin W, Tsyb AF, Stepanenko VF et al Iodine deficiency, radiation dose, and the risk of thyroid cancer. Int J Epidemiol, 2003; 32:584-91.

Soares P, Trovisco V, Rocha AS, et al.: BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. Oncogene 2003; 22: 4578–4580.

Tronko M, Bogdanova T, Biryukov A et al Thyroid cancer of Ukranians exposed as children or adolescents as a result of the Chernobyl accident. Report of the German Federal Office for Radiation Protection, 2005. BMU-2005-668, appendix 7, 1-47.

Tronko MD, Howe GR, Bogdanova TI et al A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident, J Natl Cancer Inst, 2006; 98:897-903.

WHO. Health Effects of the Chernobyl Accident and Special Health Care Programmes; Report of the UN Chernobyl Forum Expert Group ‘‘Health’’ (EHG). Geneva, World Health Organisation. 2005.

Williams ED: Effects on the thyroid in populations exposed to radiation as a result of the Chernobyl accident. In: One Decade after Chernobyl. Vienna: International Atomic Energy Authority, 1996; pp 207–230.

Williams ED, in Current Endocrine Concepts, Praeger, New York,1982, 3-10.

Williams D. Radiation carcinogenesis: Lessons from the Chernobyl accident. Oncogene, 2009; 27:s9-s18.

Williams ED, Abrosimov A, Bogdanova T, et al.: Thyroid carcinoma after Chernobyl, latent period, morphology and aggressiveness. Br J Cancer 2004; 90:2219–2224.

Yablokov A V, Oncological diseases after the Chernobyl catastrophe, Ann NY Acad Sci, 2009; 1181: 161-191.

Zablotska L B, Bogdanova T I, Ron E et al. A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident. Amer J Epidemiol, 2008; 167: 305-12.

# 6 SUMMARY

## Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts[2]

prepared by Patrick Smeesters, Chairman

### 6.1 Introduction

This chapter provides the background, summarizes the presentations and suggests potential implications of the Scientific Seminar on Issues with internal emitters, held in Luxembourg on 23 November 2010. It takes into account the discussions that took place during the Seminar and during the subsequent meeting of the Article 31 Group of Experts on 24 November 2010, although it is not intended to report exhaustively all opinions that were expressed.

### 6.2 The Article 31 Group of Experts and the rationale of RIHSS Seminars

The Article 31 Group of Experts is a group of independent scientific experts referred to in Article 31 of the Euratom Treaty which assists the European Commission in the preparation of the EURATOM Basic Safety Standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. According to the Euratom Treaty and to their Code of Ethics, this group of experts has to give priority to the protection of health, to the safety and to the development of the best available operational radiation protection. For doing so, they have to follow carefully the scientific and technological developments and the new data coming from the world of research, particularly when these could affect the health of the exposed persons.

In this context, a Scientific Seminar is devoted every year to emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. On the basis of input from the Directorate General Research of the European Commission and on information provided by individual members of the Article 31 Group of Experts, the Working Party RIHSS proposes relevant themes to the Article 31 Group which 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 RIHSS deals with the preparation and the follow-up of the seminar. Leading scientists are invited to present the status of scientific knowledge in the selected topic. 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 for members of the Group to be able to discuss the potential implications of the combined scientific results. Based on the outcome of the Scientific Seminar, the Group of Experts referred to in Article 31 of the Euratom Treaty may recommend further research, or regulatory and/or legislative actions to be initiated. The European Commission takes into account the conclusions of the Experts when setting up its radiation protection programme. The Experts' conclusions also provide valuable input to the process of reviewing and potentially revising European radiation protection legislation.

[2] The following members of the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts contributed to the preparation of this overview: A. Friedl, R. Huiskamp, L. Lebaron-Jacobs, P. Olko, S. Risica, P. Smeesters (Chairman of the WP), R. Wakeford. They were assisted by the following official of the European Commission: S. Mundigl.

## 6.3 Background and Purpose of the 2010 Seminar

Several topics in internal dosimetry remain open issues and are still the matter of debate.

This subject has already been discussed in general during the EU Scientific Seminar 2004 (EC Radiation Protection 150) and, in particular for tritium and low-energy beta emitters, during the EU Scientific Seminar 2007 (EC Radiation Protection 152). Among the general issues identified, were the limitations in the scope and the use of effective dose and the taking into account of the sometimes significant uncertainties regarding dosimetry and exposure- or dose-effects relations.

The aim of the current seminar was to review recent data and evolutions in the field.

## 6.4 Main points arising from the presentations

**Eric Blanchardon** – *The issue of dosimetry and uncertainties in the context of internal emitters*

Dosimetry in the context of internal emitters is a complex task involving measurement of activity in the environment and individuals, investigation of the conditions of exposure and application of biokinetic and dosimetric models to represent the behaviour of radionuclides in the body and the consequent deposition of energy in the radiosensitive target tissues or cells. The development of measurement techniques and the collection of scientific data enable internal dose assessments of increasing sensitivity, accurateness and reliability.

However uncertainties do still exist at each stage of the process, due to counting statistics, variable measurement efficiency, incomplete biokinetic, physical and anatomic datasets, simplified models, heterogeneous distribution of radionuclides and identification of target cells in tissues. There exists also a large inter-subject variability and a lack of direct observations for women and children. As a result, the assessment of effective dose due to a contamination from bioassay data is subject to uncertainty up to sometimes several orders of magnitude.

These uncertainties may be to some extent quantified by mathematical methods such as Bayesian inference. The harmonisation of such uncertainty assessment at the European level, its application in common situations and possible regulatory implementation represent a challenge for the years to come.

Besides, the improvement of activity measurement devices, biokinetic and dosimetric models is still an on-going process. Regarding measurement, the quality assurance through the organization of intercomparisons at the European level practically appears as a key issue. Regarding models, their complexity warrants guidance in their application, if only to remind their limitations and the unavoidable associated uncertainties. In the long term, further research is desirable to investigate the respective location of internal emitters and target regions for health effects in the human body and to link the outcome of dosimetry and microdosimetry with the observation of biological responses in the various situation of exposure.

**John Harrison** – *Risks from internal emitters and the ICRP protection system*

There are extensive data on the risks of disease, principally cancer, following exposures to external radiation but less information on risks from internal emitters, radionuclides retained in body organs and tissues following their inhalation or ingestion. The principal source of information on radiation risks that informs international standards is the follow-up studies of the survivors of the atomic bombings at Hiroshima and Nagasaki. The risk estimates derived for the A bomb survivors relates to high dose rate exposures to gamma rays. Studies of

protracted external exposures of radiation worker cohorts are of critical importance in determining the applicability of these dose estimates at low doses and dose rates. The latest analysis of the UK National Registry for Radiation Workers established a dose-response relationship for cancer consistent with the linear extrapolation of A bomb risk factors to low doses (with a DDREF of 1).

In the ICRP protection system, the risk estimates derived from the A bomb survivor studies are applied to all radiation exposures including those from internal emitters. While external exposures generally result in fairly uniform exposures of body tissues, doses from internal emitters include protracted heterogeneous exposures to short-range emissions of alpha particles and low energy electrons (eg. from plutonium-239 and tritium). Risk estimates for internal emitters that allow comparisons include lung cancer caused by radon and plutonium-239, liver cancer and leukaemia in patients given 'Thorotrast', and bone cancer from radium. The available epidemiological data on effects of internal emitters provide support for the assumption of equivalence between internal and external exposures, taking account of difference due to radiation quality. This equivalence is also supported in general by animal data and mechanistic studies. However, substantial uncertainties remain and the adequacy of protection for internal emitters continues to be questioned. A research priority must be the pursuance of all possible sources of additional epidemiological data. Worker cohorts and Russian Techa River cohorts seem currently well suited for this purpose.

A distinction should be drawn between the use of science for the calculation of doses to individuals for risk assessment purposes and for the development of a practical system of protection. Effective dose is used in the ICRP protection system as a risk-related quantity for the control of sources and radiation exposures. The calculation of effective dose to a sex-averaged reference person involves simplifying assumptions, particularly in the choice of radiation and tissues weighting factors. It enables all radiation exposures to be summed in a single quantity for comparison with dose limits, constraints and reference levels for workers or members of the public, but it does not provide best estimates of dose and risk to individuals. However, the biokinetic and dosimetric models developed by ICRP for the calculation of organ and tissue doses from internal emitters are becoming increasingly physiologically realistic. As a result, these models are well suited for adaptation to scientific applications, including the calculation of doses to individuals in epidemiological studies. An important development in this respect is the consideration of uncertainties in dose estimates.

**Dominique Laurier** – *Progress in understanding radon risk*

Radon has been recognised as a human lung carcinogen in 1988 by the World Health Organisation. The main source of information on risks of radon-induced lung cancer has been epidemiological studies of underground miners. More recently, several studies were developed to analyse lung cancer risk associated to residential radon exposures in the general population.

Recent results from miner epidemiological studies provided precise estimates of lung cancer risk associated to radon cumulated exposure. Risk coefficients provided by these low-level exposure studies are generally higher than those previously published. The resulting exposure-lung cancer risk coefficient in a European combined cohort was ERR per 100 WLM = 2.60 (95%CI= 1.83–3.36), to compare with the UNSCEAR 2006 figure of 0.59 (95%CI = 0.35-1.0) based on a comprehensive review of all available epidemiological results. The differences in the estimated ERR/WLM between whole cohorts and period-restricted or level-restricted subsets could reflect the effects of several concomitant factors: better quality of exposure assessment in the later periods, lower exposure rates and shorter time since exposure.

Recent results from miner epidemiological studies also allowed a better quantification of modifying factors of the exposure-risk relationship and of the interaction with smoking. Results confirm the major effect of time since exposure (decrease of the ERR with increasing

delay since exposure) and of age at exposure (higher ERR for exposures received at young age).

The relationship between radon exposure and lung cancer risk appears to be only slightly modified after controlling for smoking, confirming that the lung carcinogenic effect of radon persists even when smoking is adjusted for. Additional analyses provided arguments in favour of a sub-multiplicative interaction between radon and smoking, even if a multiplicative effect may be possible at low levels of radon exposure.

Consideration of these recent results from miner studies led to an increase of the estimated lifetime excess absolute risk of lung cancer death from radon and radon progeny compared to previous ICRP estimates (5 instead of 2.8 $10^{-4}$ per WLM).

There is compelling evidence from cohort studies of underground miners and from case-control studies of residential radon exposures that radon and its progeny can cause lung cancer. Comparisons of relative risk estimates between miners and residential models yielded very coherent estimates.

Collaborative works between epidemiologists and dosimetrists allowed calculation of lung dose-risk relationships (instead of exposure-risk models previously). Results confirmed the major contribution of exposure to radon decay products to the organ dose and there is currently a close agreement between dosimetric and epidemiological approaches.

Finally, it appears that the currently available results do not allow quantifying the health effects of radon in water. Nevertheless, it seems that cancer risk posed by radon in household public water supply is small and can mainly be attributed to the transfer of radon into air and the subsequent inhalation of radon decay products, rather than to ingestion of water. The risk could however be higher for people using private wells for water supply where radon levels could be high and variable.

For solid tumours other than lung cancer, and also for leukaemia, there is currently no consistent evidence of any excess associated with radon and radon progeny exposures.

Perspectives for the future include (i) continuing international epidemiological research by “pooling” of data from different countries and continents, (ii) continuing dosimetry studies in order to reduce uncertainties of organ doses (iii) getting more information to quantify the effects of exposures received during childhood (iv) identifying radon biomarkers for better classification of individuals regarding exposures, or for providing early indicators of diseases or to discriminate between standard and sensitive individuals. Finally several results published during the last years raised the issue of risks other than lung cancer potentially associated to radon. Answer to this issue requests very long follow-up periods and good control for potential confounders. The extension of the follow-up of current miner cohorts should provide new elements regarding this issue in the next 10 years.

**Serena Risica**, **Francesco Bochicchio and Cristina Nuccetelli** – *Thorium-232, the less known decay chain*

The thorium chain has undoubtedly been less studied than the uranium chain, and its health effects have been sometimes underestimated. Population exposure to couples of radionuclides from the two chains were compared, highlighting some gaps of knowledge, which shows that research activities in this area should be further encouraged.

Population exposure to $^{232}$Th or the $^{232}$Th series originates mainly from external γ irradiation and intake with the diet. As for external γ irradiation, it is significant in indoor environments where building materials contain non-negligible activity concentrations of natural radionuclides. Concerning the intake with the diet, population doses from $^{232}$Th from this pathway seem to be generally negligible, but ingestion dose coefficients of $^{232}$Th for all age classes are up to an order of magnitude higher than those of $^{238}$U. Therefore, new

investigations should be recommended, because accumulation phenomena cannot be excluded in some environmental matrices.

Very scarce data are available on $^{228}$Ra activity concentration in the diet and drinking water, even if ingestion dose coefficients of $^{228}$Ra for all age classes are up to one order of magnitude higher than for $^{226}$Ra. Moreover, $^{228}$Ra ingestion dose coefficients for children and adolescents are 5 to 8 times higher than those for adults and those for infants ($\leq$ 1 year) more than 40 times higher. Therefore, representative national surveys would be recommendable, not only to estimate natural background values and the average annual population intake more accurately, but also to highlight possible critical exposures.

Lastly, population exposure to indoor concentrations of $^{220}$Rn and its decay products may be non-negligible in buildings where soil or building material, or both, are rich in $^{232}$Th. This was recognized by UNSCEAR, however, there are still severe gaps of knowledge in both measurement techniques and dosimetry and neither international organisations (European Commission or IAEA) nor any European country have so far established clear-cut limitations of $^{220}$Rn in workplaces or indoors.

**Sir Dillwyn Williams** – *Thyroid cancers after the Chernobyl accident – lessons learnt: an update*

To date, thyroid cancer has been the main direct consequence of exposure to fallout in the population in Belarus, northern Ukraine, and the oblasts of the Russian Federation closest to Chernobyl.

Although there is no doubt that a substantial fraction of this excess incidence of thyroid cancer can be attributed to exposure to radioiodine due to the Chernobyl accident, there are several uncertainties in establishing the exact size of the increase, either as an absolute number or as an increase in incidence. This is also true for predictions of the future.

Estimates of the risk/Gy also vary greatly, particularly as the various studies performed differ in a number of ways.

Reporting an overall figure for the risk of developing thyroid carcinoma after exposure to radiation conceals the effects of a number of variables. The major one is age at exposure. There is no doubt that in the population exposed to fallout after Chernobyl the risk of developing thyroid cancer was greatest in young children (possibly with the first 3 years of life being particularly sensitive), falling rapidly with increasing age at exposure. Those exposed at a young age carry this increased risk into adulthood: the substantial increase in thyroid cancer incidence seen amongst those exposed as children or adolescents in Belarus, the Russian Federation and Ukraine since the Chernobyl accident shows no signs of diminishing up to 25 years after exposure.

Another major variable affecting risk is the level of dietary iodide. The risk for thyroid cancer in areas with severe iodine deficiency was found to be approximately three fold that in areas with normal iodide levels. Studies also showed that long term supplementary iodide intake after the accident lowered the risk in both the higher and lower iodide levels. The use of long-term dietary iodide administration in populations exposed to fallout containing radioactive iodine should then be considered, particularly in iodine deficient areas.

With increasing latency the papillary carcinomas (PTCs) that form the great majority of the radiation induced cases have become smaller, and clinically less aggressive. Molecular findings in the PTCs have also changed with latency.

The two major lessons (age at exposure and dietary intake) from studies of those exposed to the Chernobyl accident combine when considering how to express the risk of developing thyroid carcinoma after exposure to fallout. The ERR/Gy will be affected by both factors, and

it will be necessary to specify the group referred to, for example children under 3 from an iodine deficient area, rather than imply that a single ERR is generally applicable.

Another important lesson from the study of the thyroid carcinomas that have occurred as a result of exposure to fallout from the Chernobyl accident is that the morphological, clinical and molecular findings all change with increasing latency. These changes are likely to continue, and the future may see increases in follicular carcinomas of the thyroid, and possibly of other thyroid malignancies. This strengthens the case for long-term studies of this unique event.

# 7 CONCLUSIONS

## Working Party "Research Implications on Health and Safety Standards" of the Article 31 Group of Experts[3]

After discussion there was a broad consensus within the Article 31 Group of Experts on the following conclusions:

- There is generally, in the (limited) available data, a good consistency between risk and calculated internal doses.

  Nevertheless, there remain many uncertainties, sometimes large, regarding internal emitters, among which some have been highlighted, in particular:

  - the precise location of the target cells and of the molecular targets (physico-chemical properties of the source, micro-environment, …)
  - and the poor availability of relevant data for a number of radionuclides in the case of exposure of children.
- The effective dose is made for risk management rather than for risk assessment. Therefore it does not represent a best estimate of the dose and risk and quantification of the uncertainties is necessary in many cases. As underlined after the EU Scientific Seminar 2004, dose and risk estimates should be, where appropriate, combined with an appreciation and an explicit statement of the uncertainties involved. The necessary tools to do this should be largely available and this in a user friendly form.
- The risk of radon is now well confirmed and the EU policy has been strengthened in the draft of the new BSS. Research is needed regarding possible radon risks other than lung cancer.
- The thorium chain issue should be further explored and possible risk situations identified. The assessment of dose coefficients for thoron by ICRP would be appreciated.
- The particular sensitivity of small children (particularly 1 to 3 y) to the effects of radioactive iodine is confirmed and still continues in the areas affected by the Chernobyl accident. Iodine deficiency in the diet appears to play an important role too, including after the exposure. Doubts still remain regarding thyroid papillary cancer induction in those exposed as old adults. Emergency plans have to take due account of these elements, especially for protection of small children.

[3] The following members of the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts contributed to the preparation of these conclusions: A. Friedl, R. Huiskamp, L. Lebaron-Jacobs, P. Olko, S. Risica, P. Smeesters (Chairman of the WP), R. Wakeford.

MJ-XA-13-001-EN-C

Publications Office

ISBN 978-92-79-28682-7

doi:102768/22829