
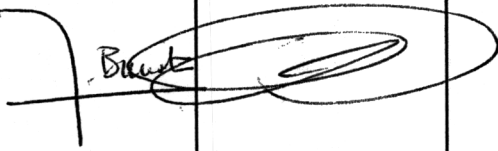

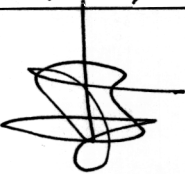


Health consequences of chronic internal contaminations by radionuclides

Comments on the ECRR report
*“The health effects of ionizing
radiation exposure at low doses
for radiation protection purposes”*
and IRSN recommendations

Requested by		IRSN Direction committee		
<p>Health consequences of chronic internal contaminations by radionuclides</p> <p>Comments on the ECRR report "The health effects of ionizing radiation exposure at low doses for radiation protection purposes" and IRSN recommendations</p> <p>Report DRPH/No. 2005-20</p>				
	Reserved for the unit		Visas for distribution	
	coordinator(s)	Checked by*	Director of DRPH	Director General of IRSN
Names	F. PAQUET	J. BRENOT	P. GOURMELON	J. REPUSSARD
Dates	08/02/05	28/6/2005	4/07/05	06/07/05
Visas				

* report under quality assurance

Individuals involved in the preparation of this report:*

P. Gourmelon (Chairman)	Institut de Radioprotection et de Sûreté Nucléaire, France
P. Barbey	Association pour le Contrôle de la Radioactivité de l'Ouest, France
J.C. Barescut	Institut de Radioprotection et de Sûreté Nucléaire, France
A. Bouville	National Cancer Institute, USA
D. Cancio	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, Spain
J.D. Harrison	National Radiological Protection Board, United Kingdom
C. Luccioni	Institut de Radioprotection et de Sûreté Nucléaire, France
C. Murith	Office Fédéral de la Santé Publique, Switzerland
J.C. Nénot	Institut de Radioprotection et de Sûreté Nucléaire, France
F. Paquet	Institut de Radioprotection et de Sûreté Nucléaire, France
F. Rollinger	Institut de Radioprotection et de Sûreté Nucléaire, France
M. Sene	Groupement des Scientifiques pour l'Information sur l'Energie Nucléaire, France
P. Smeesters	Agence Fédérale de Contrôle Nucléaire, Belgium
A. Sugier	Institut de Radioprotection et de Sûreté Nucléaire, France
M. Tirmarche	Institut de Radioprotection et de Sûreté Nucléaire, France

* This document is a report by IRSN which, in a political will to conduct pluralistic assessments, desired to expand the work group to external experts who served in their individual capacity.

<i>Preamble</i>	5
<i>I. Problems relating to internal contamination by radionuclides</i>	6
<i>II. Scientific and technical analysis of the ECRR report</i>	7
II.1. Questions raised by ECRR.....	7
II.2. IRSN analysis	7
II.2.1 - Dose-effect relationship.....	8
II.2.2 - Dosimetric variables.....	10
II.2.3 - Risk re-assessment	12
II.2.4 - Reducing approach of the collective dose	14
<i>III. Internal contamination characteristics</i>	15
III.1. Internal exposure specific features	15
III.2. Problems of chronic exposures	19
III.3. Recent radiobiology and cancerology data that may modify risk assessments ...	22
III.4. Assessment of health consequences through epidemiology.....	24
<i>IV. Conclusions and IRSN recommendations</i>	25
<i>References</i>	28

Preamble

The report published in 2003 by the European Committee on Radiation Risk (ECRR) severely criticizes part of the recommendations issued by the International Commission on Radiological Protection (ICRP), adopted by the European Directive of May 13, 1996, then by the French Government in 2002. ECRR does not call in question the system of protection against radiation when it applies to external exposures, but expresses important criticisms in the case of internal contaminations by radionuclides. The Committee considers that the current assessments of the risk involved after contamination are under-estimated and bases its arguments on works published in part in the scientific literature. Its analysis leads it to propose new risk coefficients and new dose limits, well below those adopted in the legal provisions and international recommendations.

The ECRR group raises fundamental questions with regard to radioprotection. These questions are valid and deserve a debate. Consequently, IRSN wishes to deliver its own analysis in this respect and express comments on the scientific approach applied by ECRR. For this purpose, it created a pluralistic group of national and international experts in charge of describing internal contamination phenomena, conducting a scientific and technical analysis of the ECRR report, delivering a state of the art on the knowledge acquired with regard to internal contamination and finally, expressing recommendations covering all the topics discussed. This report is targeted to questions relating to internal contamination and difficulties inherent to the assessment of risks involved after a chronic exposure. Consequently, it does not fully covers the problems relating to the radioprotection of workers and populations.

I. Problems relating to internal contamination by radionuclides

Internal contaminations result from the transcutaneous penetration of radionuclides deposited on the skin, or from their incorporation after ingestion, inhalation or injury. One of the radioprotection challenges consists in predicting the risks induced by this type of exposure. This assessment is difficult, as it requires knowing the relationships between the incorporated amounts of radionuclides and the occurrence of pathologies. The available data to determine this specific risk coefficients is limited as, most often, it is very difficult to link the observed pathologies and accurate exposure levels. In fact, the only usable data concern individuals exposed to radon-222, thorium-232 in thorotrast form, radium isotopes and finally, plutonium-239. The basic pathologies inventoried after an exposure to these radionuclides include lung, liver, bone cancers, and leukemia.

ICRP and ECRR principle positions with regard to internal contamination

The ICRP approach consists in establishing a relationship between the radionuclide incorporation levels and the incident pathologies via the dose delivered to organs, to tissues or to the whole body. The dose delivered to organs and tissues is calculated using biokinetic models that describe the absorption, the distribution and the excretion of radionuclides after incorporation. These models allow defining the residing time of a specific radionuclide in the vicinity of target cells and therefore, the dose delivered to all sensitive tissues.

The ICRP considers that the risk induced by radiation exposure is independent from the position of the radiation source. It thus considers that the risks for cancers occurring after an internal exposure may be derived from the risk coefficients calculated for populations exposed to external radiation sources, like the Hiroshima and Nagasaki survivors. This approach is confirmed by the Harrison and Muirhead study (2003), which demonstrates that the risk for occurrence of lung and liver cancers, but not leukaemias, for individuals respectively exposed to radon or to Thorotrast is, with reservations, correctly modelled by this approach.

This position is totally opposed to the ECRR position, which reminds that as the Hiroshima and Nagasaki populations were exposed to high doses generated by an external exposure and delivered over a very short moment, the corresponding risk factors cannot be applied to contaminated individuals, usually exposed to low doses resulting from chronic internal exposures. The ECRR bases its arguments on a number of sample pathologies (leukemias around Sellafield, miscellaneous diseases for children contaminated by the fallouts of the Chernobyl accident, cancers occurring after nuclear test fallouts, Gulf War syndrome, etc.) being associated with such exposures, according to some authors. The ECRR relies on these examples to state that the system proposed by the ICRP is not suitable for this type of situation, as the use of its models does not allow linking the radiation with the existing pathologies. The ECRR thus considers that internal exposure is much more harmful than external exposure, due to the incorporation of radioactive products within the cells or their components. It concludes that the risks for developing pathologies in this exposure situation are much higher than predicted by the ICRP.

Besides these positions, it should be noted that the assessment of the risk induced by internal contaminations is associated with a number of uncertainties due to the lack of data in certain domains, the complexity of dosimetric calculations, and the quality of epidemiologic investigation data. In addition, various phenomena may complexify the assessment of doses and risks, or even totally mislead the interpretations. As an example, we can mention the heterogeneous distribution of radionuclides, the validity of weighting factors applied for calculating internal doses, the impact of the radionuclide speciation on their behavior, and the chemical toxicity of certain elements. These topics will be developed further in this document.

II. Scientific and technical analysis of the ECRR report

The ECRR, which involves about 50 members, was created in 1997 to discuss the contents of the European Community Directive 96/29. In its report published in 2003, the following targets were defined:

- To independently estimate, based on its own evaluation of all scientific sources, in much details as necessary, using the most appropriate scientific framework, all of the risks arising from exposure to radiation, taking a precautionary approach,
- To develop its best scientific predictive model of detriment following exposure to radiation, presenting observations which appear to support or challenge this model, and highlighting areas of research which are needed to complete the picture,
- To develop an ethical basis and philosophical framework to form the basis of recommendations, related to the state of scientific knowledge, lived experience and precautionary principle,
- To present the risk and the detriment model, with the supporting analysis, in a manner to enable and assist transparent policy decisions to be made on radiation protection of the public and the wider environment.

II.1. Questions raised by ECRR

Various questions raised by the ECRR are quite pertinent and led IRSN to analyze this document with a pluralistic approach.

- a. Besides natural and medical exposures, populations are basically undergoing low dose and low dose rate prolonged internal exposures. But the possible health consequences under such exposure conditions are ill-known. Failing statistically significant observations, the health consequences of low dose exposures are extrapolated from data concerning exposures that involve higher dose rates and doses. Also, few epidemiologic data could be analyzed for assessing inner exposure effects. The risks were thus assessed from health consequences observed after external exposure, considering that effects were identical, whether the exposure source is located outside or inside the human body. However, the intensity, or even the type of effects might be different.
- b. The pertinence of dosimetric values used for quantifying doses may be questioned. Indeed, the factors applied for risk management values are basically relying on the results from the Hiroshima and Nagasaki survivors' monitoring. It is thus not ensured that the numerical values of these factors translate the actual risk, regardless of exposure conditions, and especially after low dose internal exposure.
- c. Furthermore, since the preparation of the ICRP 60 publication, improvements in radiobiology and radiopathology, or even in general biology, might finally impair the radiation cell and tissue response model applied to justify radioprotection recommendations. It was thus justified to contemplate the impact of such recent observations on the assessment of risk induced by an exposure to ionizing radiation.

II.2. IRSN analysis

The conducted analysis only covers the scientific aspect of the ECRR document, namely the "risk assessment", and not the "ethics and philosophy of risk management". The IRSN work group proposes to detail a number of remarks and comments, which do not intend to be exhaustive. The ECRR report includes inaccuracies, unsupported statements and various types of errors. Errors are of two types, sometimes numerical, and sometimes conceptual. Some author statements are contradictory, within the report, thus generating an inconsistency feeling for the reader. Inaccuracies are frequent, and various statements are based on simplifying and reducing assumptions.

Contrary to the rule in scientific publications, a rule applied in the appendices to ICRP 60, which support and justify the recommendations, the ECRR deliberately selected not to include references into the text. This does not allow the reader to obtain additional information or analyzing certain statements being in apparent contradiction with the international literature data. Furthermore, the list of bibliographic references is incomplete, and some data sources are not even mentioned.

The following sections describe the four major topics in which inaccuracy, inconsistency and/or conceptual error are found.

II.2.1 - Dose-effect relationship

Within the same document, it is not acceptable to state both that the linear no-threshold relationship is "patently not true" (see Box 1) and to use this relationship for risk assessments even, as the authors mention, this is an easy way to perform consequence calculations.

TABLE 5.2: FAILURE OF HIROSHIMA STUDY TO EXPLAIN OR PREDICT CONSEQUENCES OF EXPOSURE

<i>Failure mechanism</i>	<i>Notes</i>
<i>Inappropriate controls</i>	<i>Both study group and controls exposed to internal irradiation from fallout</i>
<i>Extrapolation from high dose to low dose</i>	<i>Cells killed at high dose, mutated at low dose</i>
<i>Extrapolation from acute to chronic</i>	<i>Variation in cell sensitivity following earlier exposure</i>
<i>Extrapolation from external to internal</i>	<i>External gives homogeneous doses (single tracks) whereas internal can give high doses (multiple or sequential tracks) to cells local to the source</i>
<i>Assumption of linear no threshold</i>	<i>Patently not true</i>
<i>Extrapolation from Japanese the world population</i>	<i>Different susceptibility of different populations is well established</i>
<i>Extrapolation from war survivors</i>	<i>War survivors selected for resistance</i>
<i>Begun too late and missed early deaths</i>	<i>Total yield not accurate</i>
<i>Excluded illness apart from cancer</i>	<i>Total health detriment ignored for later exposures</i>
<i>Genetic damages modeled on gross abnormality</i>	<i>Missed subtle effects, ignored sex ratio effects on birth rates</i>

Box 1: *ECRR analysis of the radioprotection model based on the Hiroshima survivors (from Table 5.2 in ECRR report 2003, page 33)*

So, the authors determine risk factors per dose unit (see Box 2) and assess the numbers of cancers based on these factors, which is an implicit recognition of a linear dose-effect relationship.

The reasoning inconsistency is also explicit in the new radioprotection system proposed by the ECRR. When calculating the number of deceased, the authors apply an ICRP risk assessment formula based on a linear no threshold relationship, in which they replace the effective dose (or equivalent) with a biological equivalent dose (see Box 3 and following section). This *de facto* implies that their final risk calculation is still based on a linear no threshold relationship assumption.

**TABLE 7.5: ICRP AND ECRR MODIFIED RISK FACTORS
FOR WHOLE POPULATION FOR WHOLE BODY EFFECTS**

<i>Outcome</i>	<i>ICRP risk factor (per Sievert)</i>	<i>ECRR risk factor (per Sievert)</i>
<i>Fatal cancer</i>	<i>0.05</i>	<i>0.1</i>
<i>Non-fatal cancer</i>	<i>0.1</i>	<i>0.2</i>
<i>Severe hereditary defect</i>	<i>0.013</i>	<i>0.026</i>
<i>Malformation after in utero exposure</i>	<i>> 0.1Gy threshold</i>	<i>No threshold</i>
<i>Cancer after in utero exposure</i>	<i>0.2</i>	<i>0.4</i>
<i>IQ lowering after in utero exposure</i>	<i>30 IQ points</i>	<i>30 IQ points</i>
<i>Severe retardation after in utero exposure</i>	<i>0.4</i>	<i>0.8</i>

Nominal probability coefficient expressed in Sv⁻¹

Note: Values for workers, where applicable, are slightly less than these owing to the different age distribution of workers. Refer to the ICRP publications for details.

Box 2: *ICRP and ECRR modified risk factors for whole population for whole body effects (from Table 7.5 in ECRR report 2003, page 58)*

7.12 CALCULATING THE FATAL CANCER YIELD IN AN EXPOSED POPULATION

If we assume, with ICRP, that the excess cancer mortality is proportional to radiation dose (the linear no threshold model LNT), then the number of cancer death that will occur in a population that is exposed to radiation is:

$$\text{Deaths} = (\text{number exposed} \times \text{equivalent dose Sv}) \times \text{Risk factor (per Sv)}$$

If the collective dose is known (in Person Sievert), then the right hand side of the equation is simplified to:

$$\text{Collective equivalent dose (PSv)} \times \text{Risk factor (per Sv)}$$

Because the ECRR has modified the calculation of equivalent dose by including weighting factors for the effectiveness of the radiation in causing mutations at the molecular level, the calculation is the same except that the biological equivalent dose is substituted. The ECRR calculation of excess cancer death would thus take the form:

$$\text{Deaths} = (\text{number of people exposed}) \times (\text{biological equivalent dose, Sv}) \times \text{Risk factor (per Sv)}$$

If the collective dose is known (in Person-Sievert), then the right hand side of the equation is simplified to:

$$\text{Collective biological equivalent dose (PSv)} \times \text{Risk factor (per Sv)}$$

Box 3: *Calculation of the fatal cancer yield in an exposed population, according to the ECRR method (from ECRR report 2003, page 59).*

II.2.2 - Dosimetric variables

One of the major ideas in the ECRR report is the incorporation of a new dosimetric variable: the biological equivalent dose. This proposal raises a number of problems.

To quantify a health detriment like the occurrence of cancers, it is necessary to correct a physical parameter, the dose, with a number of weighting factors, which allow reporting the effects of the variable effectiveness of incident radiation, and of the variable sensitivity of the tissues affected by the same deposited energy. These weighting factors may be either macroscopic, and defined from the observation of the detriment itself (for example, incidence of cancers based on epidemiologic surveys), or be based on microscopic variables that integrate biophysical, molecular and tissular mechanisms involved. The ECRR report applied the last method. This report proposes two microscopic weighting factors, w_j and w_k , one being oriented to biophysical mechanistic criteria (w_j) and the other to biochemical mechanistic criteria (w_k) (see Boxes 4 and 5). The problem with the second method, as opposed to the ICRP method which deliberately selected the macroscopic approach, is the requirement to know the quasi totality of mechanisms involved at all steps in the carcinogenesis process, from the energy deposit to the organism, in order to obtain a representative value of the health detriment. The strategy consisting in tracing the mechanism string to the sub-cellular or cellular level, such as those incorporated for determining w_j and w_k , imposes establishing a statement of the mechanisms involved being as exhaustive as possible and quantifying them to determine the numerical values of the weighting factors. The authors only incorporated some rare biophysical or biochemical mechanisms, insufficient to report the extreme complexity of radio induced carcinogenesis, and they defined the numerical values of their weighting factors over a multiple decade scale with no scientific justification for the mechanism selection or relevant numerical values.

TABLE 6.2: BIOPHYSICAL HAZARD FACTORS W_j FOR EXPOSURES IN THE LOW DOSE RANGE

<i>Exposure type</i>	<i>Factor W_j</i>	<i>Notes</i>
1. External Acute	1.0	
2. External protracted (see 3)	1.0	<i>Dose rate sparing is not assumed</i>
3. External: 2 hits in 24 hrs	10 to 50	<i>Allows for repair interception</i>
4. Internal atomic single decay	1.0	<i>e.g., Potassium-40</i>
5. Internal atomic 2nd event	20 to 50	<i>Depends on decay sequences and dose</i>
6. Internal Auger or Coster-Kronig	1 to 100	<i>Depends on location and energy</i>
7. Internal insoluble particulate	20 to 1000	<i>Depends on the activity, particle size and dose*</i>

* Tamplin and Cochran (1974) gave the enhancement of dose for Plutonium oxide hot particles as high as 115,000.

Box 4: Biophysical hazard factors W_j as determined by the ECRR (from Table 6.2 in ECRR report 2003, page 42.)

TABLE 6.3 : SPECIFIC INTERNAL ISOTOPIC BIOCHEMICAL ENHANCEMENT FACTORS W_K

Isotope or class	Factor W_K	Mechanism of enhanced effect
3-H; Tritium	10 to 30	Transmutation and local dose; hydrogen bonding; enzymatic amplification
Ionic equilibria cations, e.g. K, Cs, Ba, Sr, Zn	2 to 10	Local concentration by interfacial ionic absorption; depends on effect considered
DNA binding, e.g. Sr, Ba, Pu	10 to 50	DNA primary, secondary and tertiary structure disruption
14-C	5 to 20	Transmutation and enzymatic amplification
35-S, 132-Te	10	Transmutation and enzymatic amplification; hydrogen bonding
Enzyme and co-enzyme seekers, e.g. Zn, Mn, Co, Fe	10	Enzymatic amplification
Fat soluble noble gases, e.g. Ar-41, Kr-85	2 to 10	Depends on effect considered
Barrier transmutation series, e.g. Sr-90 Y-90	2 to 1000	Depends on effect considered

Box 5: Biochemical hazard factors W_K as determined by the ECRR (from Table 6.3 in ECRR report 2003, page 43.)

Furthermore, in the formula expressing the biological equivalent dose and the biological effective dose (see Boxes 6 and 7), the authors multiply an ICRP macroscopic variable obtained from the results of epidemiologic surveys, with microscopic variables w_j and w_k , which by definition, is a conceptual error and destroys the system consistency.

The biological equivalent dose B in tissue T resulting from the specific exposure E of quality R is given by the expression:

$$B_{T,E} = \sum_R N_E H_{T,R}$$

where $H_{T,R}$ is the absorbed dose averaged over the tissue or organ T , due to radiation R , and N_E is the hazard enhancement weighting factor for the specific exposure E .

N_E is made up of a number of hazard enhancement factors associated with different processes leading to genetic mutation and other relevant biological damage. For each type of exposure from each internal source S , there will be assumed to be a weighting for the hazard associated with that exposure. This weighting is made up of biophysical and biochemical factors which are multiplicative since probabilistically they are deemed to be non-independent binomial factors which act on the same mechanisms (DNA mutation). Thus:

$$N_E = \sum W_J W_K$$

In the case of J different biophysical aspects of the specified exposure and K different aspects of the internal exposure which the committee believes carry enhanced risk of injury.

Box 6: Biological equivalent dose, as defined by ECRR (from ECRR report 2003, page 41).

The effective dose is the sum of the weighted equivalent doses in all the tissues and organs of the body:

$$E_T = \sum_T W_T H_T$$

where H_T is the equivalent dose to tissue or organ T and W_T is the weighting factor for tissue T . The effective dose can also be expressed as the sum of the doubly weighted absorbed dose in all the tissues and organs of the body.

The ICRP system for effective dose has also been adopted by the present committee with the replacement of the ICRP's equivalent dose with the new biological equivalent dose defined in 6. Thus:

$$E_T = \sum_T W_T B_T$$

E_T is strictly the biological effective dose...

Box 7: Biological effective dose, as defined by ECRR (from ECRR report 2003, page 44).

II.2.3 - Risk re-assessment

The incorporation into the ECRR report of a new dosimetric variable (biological equivalent dose) when assessing the risk would have required a re-assessment of the risk coefficients per dose unit, based on results from animal experiments or pertinent epidemiologic surveys, i.e. after internal exposure. Indeed, an increase in the numerical value of the dose mathematically results in an equivalent decrease in the risk coefficients per dose unit, with in final a mere cancellation of the risk re-assessment.

As an example, when calculating the biological equivalent dose in case of internal exposure, the ECRR proposes dose correction factors (w_j and w_k) that may vary from 1 to 1,000,000 (1,000 x 1,000 in the case of Sr hot particles), thus resulting in a noticeably high biological equivalent dose with regard to the dose delivered by a gamma radiation in external exposure. When applying this biological equivalent dose, which may reach noticeable values, to an internal exposure situation in which the health impact was scientifically established (for example, death due to radio-induced cancers determined via an epidemiologic survey), the risk coefficients per dose unit defined by the simple ratio: number of cancers / equivalent dose, are decreased by a ratio equal to the numerical value of the correction factors. Also, when the number of radio-induced cancers in animal experiments in internal exposure situation is determined and set to specific values, using the biological equivalent dose, increased by the application of these factors will *de facto* decrease the risk coefficient per dose unit.

TABLE 12.1: RISK FACTORS FOR INFANT, EARLY NEONATAL, STILLBIRTH AND BIRTH RATE DEPRESSION

<i>Birth effect</i>	<i>Percentage increase in baseline rate per mSv (ECRR)^c parental exposure in year of conception</i>	<i>Observed excess number per thousand live births 1963 per mSv (ICRP)^d parental exposure</i>
<i>Infant (0-1 year) mortality</i>	0.05 %	21 increase to 24 = 3
<i>Neonatal (0-28 days) mortality^a</i>	0.07 %	13 increase to 16 = 3
<i>Stillbirth^a</i>	0.04 %	13 increase to 17 = 4
<i>birth rate depression</i>	0.05 %	-

a. based on Sr-90 exposure to parent in 1963, in England and Wales;

b. based on fall in birth rate in Finland and parts of the UK after Chernobyl;

c. dose calculated according to ECRR model and including new weighting factors W_j and W_k ;

d. dose calculated at the time using ICRP model.

Box 8: *Risk factors, determined by ECRR, for infant and neonatal mortality (from Table 12.1 in ECRR report 2003, page 123).*

For example, for genetic effects:

24 - 21 = 3 infant deceased in excess, for a 1 mSv dose estimated with the ICRP coefficients (see Box 8).

As an example, if we consider that such exposure is partly due (0.5 to 50%) to strontium, it is possible to calculate the corresponding biological equivalent doses, applying a 300 weighting factor, as specified in the ECRR document (see, for instance, Table 13.1, page 131 and calculation of the number of cancers in Belarus):

Dose % due to Sr	ICRP dose (mSv)	ECRR dose (mSv)
0	1	1
0.5	1	$0.995 + 0.005 \times 300 = 2.5$
1	1	$0.99 + 0.01 \times 300 = 4$
10	1	$0.9 + 0.1 \times 300 = 30.9$
20	1	$0.8 + 0.2 \times 300 = 60.8$
50	1	$0.5 + 0.5 \times 300 = 150.5$

If we calculate the excess relative risk (ERR), here being equal to $(24 - 21) / 21 = 0.143$ per dose unit (mSv):

Dose % due to Sr	ICRP estimate		ECRR estimate	
	Dose (mSv)	ERR per mSv	Dose (mSv)	ERR per mSv
0	1	0.143	1	0.143
0.5	1	0.143	2.5	$5.7 \cdot 10^{-2}$
1	1	0.143	4	$3.57 \cdot 10^{-2}$
10	1	0.143	30.9	$4.6 \cdot 10^{-3}$
20	1	0.143	60.8	$2.35 \cdot 10^{-3}$
50	1	0.143	150.5	$0.95 \cdot 10^{-3}$

As a conclusion, in the system proposed by ECRR, the excess relative risk per mSv drops from 0.143 to $0.95 \cdot 10^{-3}$ when the dose is re-assessed using the new coefficients, which appears to be opposed to the ECRR desire to re-assess the risk. This topic should be discussed with this Committee.

II.2.4 - Reducing approach of the collective dose

The authors intensively use the collective dose variable, with often reducing assumptions. The calculation of the number of cancers induced by the Chernobyl accident in Belarus is an example, due to the dose levels and exposure duration used (see Box 9).

In a report commissioned by the Belarus Ambassador to the UK, Busby has recently used the fallout yield of cancers in Wales to approximate an increase in fatal cancer rate in Belarus of 50%, or 25,000 extra fatal cancers a year in the population of 9,800,000 due to exposures in the first five years following the accident.

For Belarus, the Committee has partitioned the dose given by UNSCEAR 1993 amongst individual radioisotope exposures and applied the weightings for internal excess risk given in chapter 6. The Committee made an approximate calculation as follows. The first year average committed effective dose to Belarus was given by Savchenko as 2 mSv. If this is extrapolated to five years and one third of the dose is weighted as Sr-90 or hazardous particulates, the ECRR calculation results in a ECRR model cumulative dose of about 900 mSv and a fatal cancer yield of 882,000 cases which the committee assumes will express over 50 years which is 17,640 extra fatal cancers per year, roughly in line with Busby's calculations. The 70 years overall yield is 1,200,000 in Belarus alone. The same approach to the global figures estimated by UNSCEAR suggests that the overall 70 year global cancer mortality yield following Chernobyl is in excess of 6 million.

Box 9: *Calculation, according to the ECRR method, of the number of cancers due to the Chernobyl accident (from the ECRR report 2003, page 134).*

- Considering the highly heterogeneous distribution of the surface contamination, which may also be underestimated, it is not acceptable to reason in terms of average dose for the whole population.
- Furthermore, it is impossible to consider that one third of the dose is due to strontium for the whole Belarus population, considering the strontium dispersal over a limited area around the Chernobyl plant with, in addition, a low population density (Figure 1: UNSCEAR 2000).
- The extrapolation over 5 years of the dose received during the first year is not justified. Indeed, during the first year, short life radionuclides, especially iodine isotopes, highly contributed to the received dose. But, the exposure of populations living in the contaminated territories will persist for more than 5 years.
- Furthermore, the new weighting factor for strontium was considered as equal to 300, i.e. 25 times the weighting factor for alpha emitters, without justifying this value with scientific data.

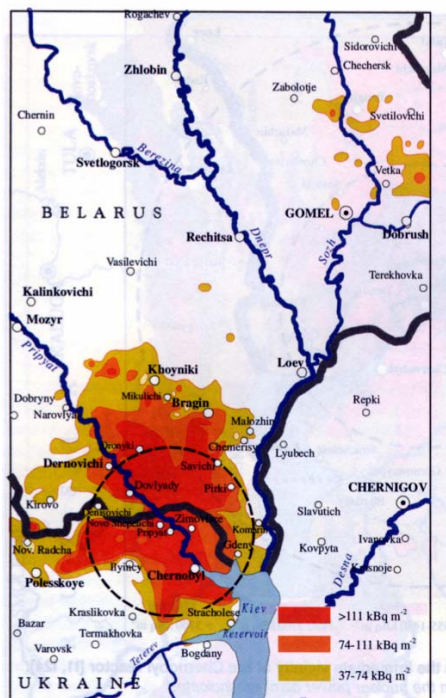


Figure 1: Strontium distribution around the Chernobyl plant (from UNSCEAR 2000)

III. Internal contamination characteristics

III.1. Internal exposure specific features

Problem of the heterogeneous distribution of radionuclides

One of the major problems relating to internal contamination by radionuclides is due to the heterogeneity of deposit in tissues. These specific deposits may be due, either to a radionuclide concentration in certain tissues or cells after incorporation and transfer to the systemic compartment (example of uranium in kidney lysosomes or neptunium in liver cell nuclei (Paquet *et al.*, 1996, Galle, 1997, Boulhadour *et al.*, 1997), or directly to inhalation and deposit of insoluble particles in lungs (hot particles). These particles consist of fission and activation products and some were scattered after the Chernobyl accident. In the case of alpha, beta and Auger emitter radionuclides, these phenomena may result in highly heterogeneous energy deposits within tissues. This may induce consequences, both on the estimate of the dose delivered to the organ target cells and on pathologies induced by an internal contamination.

Dosimetry of radionuclide heterogeneous deposits

The ICRP proposes calculating an absorbed dose by averaging the energy delivered to the whole organ. This approach is recommended for most tissues, as the ICRP states the simplifying assumption that radionuclides and target cells are uniformly distributed. An exception is accepted for bone tissue, respiratory and digestive systems, for which it is recognized that radionuclides may be heterogeneously distributed (ICRP, 1989). At the time of these publications, these recommendations incorporated the state of knowledge in radiotoxicology. At present, this reasoning may be criticized, as we are now aware that numerous radionuclides are highly heterogeneously distributed among all tissues. On the other hand, a stringent calculation of the dose to target cells would require accurately knowing both this distribution and the location of target cells, and everybody recognizes that the knowledge on this subject is failing (ICRP, 1989).

Biological effects of radionuclide heterogeneous deposits

The ECRR considers that particle concentrations in tissues, locally generating high radiation doses, are more carcinogenic than when the same amount of energy is uniformly deposited in the tissues. A set of studies, basically conducted with *in vitro* systems, appears to confirm this assumption (Lang *et al.*, 1993 ; Servomaa and Rytomaa, 1990, Likhtarev *et al.*, 1995 ; Sigg *et al.*, 1997). Other studies, based on experimental and on epidemiologic data, appears to demonstrate the contrary (Charles *et al.*, 2003). In the latter studies, the authors however recognize that human data are failing and are limited first to cancers occurring after exposure to plutonium aerosols and second, to liver cancers and leukemias that occurred after thorotrast administration for diagnostic purposes. In both cases, the radionuclide deposit was highly heterogeneous in cells, but did not appear to have significantly increased the cancer risk.

The general conclusion that may be derived is that the discussion on this topic is not closed, even if it is justified to think that human data are more pertinent than data obtained *in vitro* on cell populations. Furthermore, it is usually admitted that a high concentration of alpha emitters in a cell has a lethal effect and thus prevents from developing a cancer. On the other hand, this data remains limited in number, contradicted by recent data, and additional studies should be conducted before delivering a final conclusion.

RBE and weighting factor w_R

The probability for appearance of stochastic effects depends on the absorbed dose, but also on the radiation type and energy. This point is especially important in the case of internal exposures, and it was considered by the ICRP, which weights the absorbed dose with a factor reflecting the radiation noxiousness. This factor is known as the weighting factor for radiation and is expressed by the abbreviation w_R . The ICRP selected the values of this weighting factor to be representative of the relative biological effectiveness (RBE)¹ values for the radiation. The ICRP thus defined w_R values for photons, electrons, neutrons, protons and alpha particles (ICRP, 1990).

The ICRP position consists in basing the weighting factors on the risk for appearance of stochastic effects (ICRP, 2003). It considers that the w_R values are the same for all tissues, while acknowledging that no radiobiological data is supporting this concept. It also considers that these factors do not vary with the photon, electron, proton and alpha particle energy. An exception is accepted for neutrons, for which the values differ depending on the energy (ICRP, 1990).

¹ RBE : Relative Biological Effectiveness: Ratio of the reference radiation dose (X-rays, ⁶⁰Co gamma radiation) to the studied radiation dose generating the same biological effect. This concept was created to attempt to report the relative efficiency of the various types of radiation in living material. This concept is not applied directly in the regulatory system that uses weighting factor w_R , attributing a specific value to the various types of radiation.

The values of this weighting factor are of major importance, as they define the dose received by a tissue² and therefore, *in fine*, the risk for the contaminated individual to develop a pathology. These values are based on the state of knowledge in biophysics and radiobiology, and may thus evolve. The ICRP acknowledges that these values are affected by a number of uncertainties, especially for neutrons, and alpha particles (ICRP, 2003).

The question on this topic should thus be raised and highlights the general problem of determining the radiation biological effectiveness (RBE). The RBE concept assumes that effects are quantitatively different among radiation types, but not qualitatively. Recent studies criticize this reasoning by demonstrating that radiation with a low linear energy transfer (LET)³ may induce different effects on DAN than those generated by radiation with a high LET. Similarly, the compilation of literature data seems to demonstrate that the RBE may vary, depending on tissues, from 2 to 8 (Barnhart and Cox, 1979 ; Thacker *et al.*, 1982 ; Chen *et al.*, 1984 ; Schwartz *et al.*, 1992) and thus, that the ICRP position ($W_R = 20$ for alpha emitters in all tissues) is erroneous. Also, it was demonstrated that the RBE for tritium beta emitters was higher than 1, meaning that the ICRP position ($W_R = 1$) was underestimated. This point will have to be verified in the future, as it might impair a number of assumptions.

The RBE may also be very difficult to determine when the dose distribution is not homogeneous (see above). These examples make dosimetry difficult and, for low penetration radiation, it is essential to accurately know the position of target cells.

Finally, the difficulties met to determine the RBE are due to the fact that human data is available only for certain alpha emitters, such as radon decay products, radium, and more recently, plutonium. No human data is available for assessing the RBE for neutrons and heavy ions, and the knowledge acquired in experimental systems have to be extrapolated to the human being.

Problem of radionuclide speciation and chemical toxicity

Influence of speciation on biokinetics and compound dosimetry

The speciation of radionuclides corresponds to their physical and chemical form. This may vary with the environmental conditions and change after incorporation into the organism. The speciation influences both the distribution of radionuclides in the human body and their toxicity.

The ICRP acknowledges that radionuclides incorporated by ingestion may be more easily absorbed than non-organic forms (ICRP, 1989). Similarly, it is well known that the chemical form of inhaled compounds influences their solubility and thus, their transfer to the systemic compartment. The relevant data are integrated into the latest ICRP biokinetic models, which allow calculating the dose resulting from radionuclide incorporation. On the other hand, these data are most often limited and do not integrate all the chemical forms met in the environment or at workstations. In addition, the speciation of an element in the human body influences its retention and excretion. It was thus demonstrated that most actinides are carried in the blood bound to the plasmatic transferrin and that the stability constant of the complexe formed is inversely proportional to the distribution speed in target tissues and to their urinal excretion (Durbin *et al.*, 1997). Conversely, these elements tends to store in the tissues possessing transferrin specific receivers. This phenomenon thus influences the retention times in tissues and thus, the absorbed dose.

In addition, the speciation of a radionuclide in the human body may influence its toxicity and thus the development of pathology. Recently, studies on the interactions between uranium and kidney cells (LC-PK1) demonstrated that the $UO_2(CO_3)_2^{2-}$ complex, once inside the cytoplasmic compartment, was stored as uranyl phosphate needles and induced a toxic response depending on the concentration (Mirto *et al.*, 1999). On the contrary, uranium incorporated as citrate did not store and induced no toxicity, regardless of the concentration used. This phenomenon is not specific to radionuclides, and all metals are concerned. This point is well known and is modeled in toxicology and ecotoxicology. The difficulty met is due to the fact that few data concerning the speciation of radionuclides are available and cannot, at present, be used in dosimetric models. This phenomenon

² In this case, the dose is a risk management unit, not a physical unit.

³ LET: Linear Energy Transfer: defined as the amount of energy lost per unit of path length.

should be carefully studied, as it may noticeably modify the toxic response of an element and therefore impair the assessment of the risk associated with internal contaminations.

Radionuclide chemical toxicity

The radioprotection system is based on the dose-effect relationship, which only considers the radiological component of radionuclides. In case of internal contamination, radionuclides are incorporated and first constitute a chemical body with the property to emit radiation. Most internal contamination cases concern very small masses of radionuclides, which respond as trace elements, whose concentration in the organism is negligible. However, in some cases, the contamination level is enough for the incorporated masses to become significant and for the problem of chemical toxicity arises for these elements. This is the case for uranium, well known to induce kidney injuries from a $3 \mu\text{g}\cdot\text{g}^{-1}$ concentration in the organ (Leggett, 1989). Like neptunium, beryllium and lead, this element seems to generate numerous inclusions in the liver or kidney cell nuclei, which significance is not yet known (Berry *et al.*, 1987; Boulhadour *et al.*, 1997; Ceruti *et al.*, 2002).

The chemical toxicity of radionuclides is at present ignored and should be integrated into the radioprotection models, as it may aggravate or complicate pathologies induced by an internal contamination.

Example of problems met when assessing risks after internal exposure: case of Radon and Auger electrons

Radon is a radioactive ubiquitous gas, concentrated in the uranium mines and in dwelling built on uraniumiferous grounds. The problems raised by radon are especially important as the exposure to radon and to its solid radioactive daughter products corresponds to approximately 40% of the total dose for the population (UNSCEAR, 2000).

The assessment of the risk associated with exposure to radon, was traditionally conducted according to two approaches. The first, epidemiologic, approach, is based on the study of cohorts of uranium miners and the development of pathologies is studied in relation to the radon exposure level. In the second, dosimetric, approach, the dose to lung is calculated using the ICRP models, then compared with a risk scale basically based on the Hiroshima and Nagasaki data. The models applied for calculating the dose to lung require numerous information, such as the characteristics of radon and decay products (size of particles, solubility, etc.), and the reference parameters for the exposed population (ventilation rate, lung morphometry, location of target cells, etc.).

The joint application of both approaches shows that their results, in terms of risk for development of lung cancer in an exposed population vary by a factor 3 ($4 \text{ mSv}\cdot\text{WLM}^{-1}$ with the epidemiologic approach against $15 \text{ mSv}\cdot\text{WLM}^{-1}$ with the dosimetric approach⁴).

Auger electrons are emitted by some radionuclides, some of which, like ^{125}I , are particularly incorporated at the DNA level. Authors pertinently highlighted that these electrons should have very high RBE, due to their emission within the DNA. Indeed, recent studies demonstrate that the RBE of Auger electrons may vary from 1.5 to 40, depending on the radionuclides and measured effects (Kasis *et al.*, 1988). These figures are quite different from the weighting factor applied for electrons (equal to 1) and confirm that Auger electrons should undergo a specific assessment. The major problem is due to the fact that the knowledge on this topic is scattered and that numerous physiological and biophysical data should be acquired with regard to incorporation, inter-cellular location, and turn-over of radionuclides emitting Auger electrons.

⁴ WLM: Working Level Month. A Working Level (WL) corresponds to the concentration in 1 liter of air, of the radon decay products with a potential energy equal to $1.3 \times 10^5 \text{ MeV}$. The WLM corresponds to the WL product by a monthly working time equal to 170 hours.

Both examples emphasize the numerous uncertainties relating to risk assessment and, in particular, uncertainties due to the weighting factors for alpha particles. They demonstrate that the internal exposure problem is difficult to handle and justifies certain questions. The difficulty will be to obtain the suitable replies, while knowing that usable data in this domain is limited and that building a radioprotection system requires numerous approximations.

III.2. Problems of chronic exposures

In this report, a chronic exposure may be defined as a protracted exposure to radiation. Such exposure may be external or internal; only the second case is discussed here.

Chronic internal exposures concern all human beings. Throughout their life, individuals are exposed to radionuclides that are naturally present in the air, drinking water and food. They actually concentrate a number of elements, including ^{40}K , ^{14}C , uranium and thorium, which permanently irradiate the human body.

Chronic exposure to artificial radionuclides concerns workers in industrial plants, universities and hospitals, and public living in territories with various levels of contamination by radioactive products generated by human activities (mining, releases to the environment, military operations, nuclear accidents, etc.).

III.2.1. Chronic exposures as considered by the ICRP

The chronic exposures are only partially mentioned by the bodies in charge of radioprotection problems and radiation effects, such as ICRP or UNSCEAR (UNSCEAR, 1994; ICRP, 1999). The ICRP considers that chronic exposures only concern the public and discusses only "controllable" exposures, i.e. whose level may be decreased via protection actions, thus excluding all radionuclides having a metabolic action in the human body (^{40}K , for instance).

The ICRP considers that the best tool for assessing chronic exposures is the yearly individual effective dose, which sums up the external and internal doses received within 1 year, and should not exceed 1 mSv per year for individuals in the public. The method applied for calculating the dose resulting from the radionuclide incorporation is based on biokinetic models, which describe the behavior of radionuclides after incorporation. The ICRP considers that a chronic dose is equivalent to the sum of acute exposures (ICRP, 1995). It thus recommends to iteratively use the retention and excretion functions defined for acute exposures, to calculate the dose resulting from a prolonged exposure, and to sum up the doses resulting from various exposure sources (ICRP, 1997 and 1999).

The ICRP also considers that deterministic effects⁵ cannot occur before a protracted exposure to doses exceeding $0.5 \text{ Gy}\cdot\text{an}^{-1}$, although for certain more sensitive organs (lens of the eye, bone marrow), this level may be $0.4 \text{ Gy}\cdot\text{an}^{-1}$ (ICRP, 1990). It concludes that, in most cases, the yearly individual effective doses resulting from chronic exposures will always be less than the thresholds at which deterministic effects occur and that, consequently, the stochastic effects⁶ only will be observable.

⁵ Deterministic effects: Early noxious effects of radiation on living tissues (death of an organism, lesions to organs or tissues, cataract, etc.), which usually occur above a dose threshold and whose severity depends on the absorbed dose level. They usually occur soon after irradiation (hours, days or weeks following the received dose).

⁶ Stochastic effects: Late noxious effects induced by radiation (leukemias, tumors, for instance), whose severity is independent from the dose and development probability is proportional to the received dose. It is assumed that no threshold dose below which stochastic effects will not occur is defined. Stochastic effects thus occur for doses lower than the doses producing deterministic effects and may develop after a long period (years, decades) following irradiation.

III.2.2. System limitations

The ICRP system implies that absorbed radionuclides have no synergetic action and that the exposure duration does not impact the radionuclide biokinetics (ICRP, 1995). These statements are highly contested in ecotoxicology and in human toxicology, where it is recognized that first, the absorption and behavior of certain metals in the organism are highly depending on the presence and concentration of other chemical elements, second that the exposure duration is correlated with the age of individuals, the result of which is to modify certain physiological and metabolic functions that may in turn modify the type of toxic response (WHO, 1978).

In addition, the ICRP has very few data available for assessing the detriment induced by chronic exposures. The thresholds above which effects may occur were thus extrapolated from data obtained with patients who received protracted doses during radiation treatments, and completed with animal data (ICRP, 1999). This implies that data obtained from external irradiations may be extrapolated to internal contamination, and this is not yet the case (see section III.1).

III.2.3. State of knowledge in radiotoxicology

Data relating to the influence of chronicity on the behavior and toxicity of radionuclides are contradicting. This is partly due to the fact that this theme covers two different problems that should be handled separately. The first problem is to determine the influence of the radionuclide exposure duration. This can only be handled through experiments. The point is to compare the effects of an acute administration to the effects of a chronic administration of the same final amount of radionuclides. In this case, the conclusions most often stated result in the absence of noxiousness of chronic exposures, due to the lower amount of radionuclides delivered each day.

The second problem is to analyze the effects of a permanent exposure to radionuclides, and to compare such effects to a reference level, which is usually associated with natural irradiation. These studies are typically processed through epidemiology and may be completed with laboratory studies. This situation is inverse of the previous one as, in this case, the amount of ingested or inhaled radionuclides gradually increases in time. This specific point was widely used by certain associations or media (Kempf, 2003) to conclude that chronic exposures were noxious.

The common point in both problems is that they were widely neglected by the scientific community. In the first case, it was stated that acute contaminations by radionuclides - which were widely studied out - anyway result in a prolonged internal exposure and that chronic contamination situations do not need to be specifically studied. This argument is exact, but is applicable only for radionuclides with a long biological half-life ($T_{b1/2}$) in the organism. This is consequently true for most actinides ($T_{b1/2}$ ranging from 2 to 50 years) (ICRP, 1995), but not for other radionuclides like cesium, iodine or strontium ($T_{b1/2}$ ranging from 2 to 110 days) (ICRP, 1993).

In the case of epidemiologic studies, many thought it was possible to extrapolate the knowledge acquired with the Hiroshima and Nagasaki data to chronic internal contamination situations. The Chernobyl accident, which played a disclosing part in this respect, demonstrates that the situation is not so simple.

The statements delivered during the past years might thus be revised. The first reason is that it is now obvious that the toxicity of an element is a complex variable that partly depends on the product, its concentration in the organism, and its residence time. In this respect, it was postulated for long that the incorporation of 100 Bq in 1 day was equivalent to incorporating 1 Bq over 100 days. This is perfectly true in mathematics, but totally wrong in biology. The second reason is that reference is increasingly made to certain publications that state that the ingestion of contaminated food in the Belarus territories resulted in a high number of pathologies and malformations of any type within the population (Bandazhevsky, 2001). Even through they are not accepted by the international scientific community, these works contribute to maintaining a doubt in the public mind and should be complemented.

Influence of chronicity on the biokinetics of incorporated radionuclides

The difficulty to clearly settle this debate is due to the fact that researches conducted in this domain are very rare. At experimental level, some studies attempted to compare the kinetics of the same amount of radionuclides after an acute or chronic exposure. It was thus demonstrated that the lung clearance for nickel oxide in the rat was inversely proportional to the exposure duration (Benson *et al.*, 1992). Also, the excretion of ^{90}Sr for individuals contaminated over tenths of years in the vicinity of the Techa River, appears to be much slower than the excretion measured for individuals subject to an acute contamination (Leggett *et al.*, 1982; ICRP, 1993; Shagina *et al.*, 2003). Finally, it was demonstrated that, for the rat, chronic exposures to plutonium in drinking water may result in a specific deposit on teeth, which was not observed after an acute exposure (Renaud Salis *et al.*, 1990).⁷

Influence of chronicity on the toxicity of incorporated radionuclides

Modifications to the biokinetics of radionuclides should be considered as the precursor of a possible toxicity. It should be noticed that studies conducted in this respect are even fewer. Among the most serious, we can mention the studies conducted on dogs contaminated via intravenous injection of ^{239}Pu citrate (Lloyd *et al.*, 2001). The authors of this study demonstrated that, for an equivalent dose, repeated plutonium injections generated more cancers than one injection.

Other studies conducted in this domain concern populations being chronically exposed to a contaminated environment. In this case, most data are obtained from studies conducted on uranium miners and on civilian populations exposed to a naturally (New Mexico, (USA); Canada, Southern Finland) or accidentally (Savannah river, Techa river, Belarus) contaminated environment.

The most mediatized studies state numerous pathologies for the Belarus inhabitants, concerning the cardiovascular, central nervous, digestive, respiratory, immune, breeding systems, as well as thyroid and kidneys (Bandazhevsky, 2001). The author connects these pathologies to a permanent exposure to ^{137}Cs present on the territory. Other non contested studies state a significant increase in thyroid cancers for children in the three countries being most contaminated (Belarus, Ukraine, Russia; UNSCEAR, 2000). In this respect, it should be noticed that exposures to iodine were brief, due to the short effective half-life of ^{131}I , which is not the case for ^{137}Cs . Besides the Chernobyl accident and its impact, studies conducted in Canada seem to demonstrate that the chronic ingestion of water naturally containing uranium (2 to 781 $\mu\text{g}\cdot\text{L}^{-1}$) affects the kidney function and results in an increase of the urinal glucose concentration (Zamora *et al.*, 1998). Finally, very recent studies seem to indicate that uranium administered daily to mice through ingestion of a contaminated drinking water with levels close to maximum levels naturally existing in Finland, modifies the genetic expression in the animals' kidneys, while uranium concentrations at such level are said to be non toxic (Taulan, 2003).

The interest of all these studies lies in the fact that they demonstrate or seem to demonstrate effects that were not suspected before, when using only the Hiroshima or Nagasaki experience or acute experimental contaminations of animals. Even though the data available on this topic are partial, this seems to mean that the chronicity influences the toxicity of radionuclides.

7

*Mechanisms involved in these phenomena remain assumptions. The most probable events would be events relating to an effect of the incorporated amount that would be higher in the case of an acute contamination and would saturate some carriers at all levels of the organism (entrance, blood, storage organ), then bypass the excess to other metabolic channels. This phenomenon was often demonstrated both at the organism level and at the cellular and intracellular level (Paquet *et al.*, 1996). In the case of actinides and blood, a saturation of the main carrier, which is transferrin, would basically leave most radionuclides in an ultrafilterable form, which would then be excreted via the urine. On the contrary, in the case of a chronic contamination with a lower radionuclide level, this saturation would not occur and would result in a higher deposit in the target organs and thus, in different retention rates. Similarly it is well known that the cell lysosomes are in charge, among other things, of storing most of the exogenous products as deposits. Therefore, a chronic contamination would result in gradually concentrating radionuclides in these structures and in generating bioaccumulation phenomena, different from those observed after an acute contamination.*

Consequently, researches on this topic should be promoted in order to better determine these effects and to tighten the radioprotection system. These researches also demonstrate that the distribution of the dose in a tissue is an important fact to know, but also that the dose rate and the problem of repeated exposures for organs and tissues should be a key problem to be studied out in the future years.

III.3. Recent radiobiology and cancerology data that may modify risk assessments

The current radioprotection principles are based on a simple biological model. The DNA is considered as the major target of ionizing radiation and two-strand breaks are the critical lesion.

A cell impacted by a radiation may perfectly repair the lesions and return to its original state. If DNA lesions are too many, they may not be repaired and this will result in the cell death; deterministic effects of lesions to tissues and organs occur when the number of killed cells is very high. Finally, the cell may imperfectly and/or incompletely repair the DNA lesions and thus survive with modifications to its genetic patrimony, which would generate stochastic effects (cancers and hereditary effects), as these alterations are a first step to the cancerous conversion for somatic cells and may be transmitted to the descent when occurring in germinal cells.

It is possible to set exposure limits in order to avoid deterministic effects occurring for a high dose above a specified threshold. The stochastic effects thus represent the major risk to be managed under normal conditions.

The probability, low but non null, for a cell carrying modification(s) of the genetic patrimony, to generate stochastic effects was used for justifying the linear no threshold relationship. But, certain recent observations in radiobiology and radiopathology, most of them being conducted after the preparation of ICRP 60, result in complexifying this basic model, which might in final lead to a re-assessment of the risk induced by exposure to ionizing radiation. In fact, the analysis of the scientific literature emphasizes two totally opposed theories:

1. Certain observations suggest that the effect of exposure to low doses is less than the effect predicted from the effects induced by high doses. The dose-effect relationship would in this case be infra linear and might even include a threshold:
 - In certain experimental models, after exposures to low doses, the incidence of tumors is less than the spontaneous rate. However, extrapolation to the human being of experimental carcinogenesis data should be considered with an extreme caution, as this data allowed a comparative study of the effectiveness of the various radiation types, but not a direct quantification of the risk. Furthermore, the results of epidemiologic studies for the human being revealed numerous discrepancies. This phenomenon of hormesis even led certain authors to suggest a beneficial effect of low ionizing radiation doses.
 - The role of the cell micro-environment on the phenotype of cells, even "initiated", challenges the assumption according to which a cancer results from a DNA alteration in a cell. Indeed, experimental results, some of which were published some years ago, highlight the role of interactions between cells and the environment; they suggest a tissue and not only cell origin of cancer (Barcellos-Hoff, 2001; Park *et al.*, 2000; Hanahan and Weinberg, 2000, Krtolica and Campisi, 2002).
 - The influence of the adaptive response in the case of population exposure is more difficult to understand. Theoretically, it might result in a risk reduction, because the consequences of a high dose irradiation (frequency of mutations, chromosomal alterations, etc.) are less important if the cell was previously subject to a low dose irradiation (Rigaud and Moustacchi, 1996; Rigaud, 1999). However, the adaptive response assumes a repeated irradiation and in addition, this phenomenon does not concern all parameters: survival, mutations, chromosomal aberrations in a cell line; furthermore, to observe an adaptive response, very strict conditions, dose and dose rate for the induction irradiation and time interval between both irradiations, should be applied.

2. On the contrary, other observations suggest that the risk induced by exposure to ionizing radiation at low doses is under-estimated; the effect might be higher than predicted by the reference model, with the dose-effect relationship being, in this case, supra linear:

- Numerous cell lines show indeed an hyper sensitivity to low dose resulting in a cell survival for doses below 0,5 Gy lower than expected by a simple extrapolation of the observed survival rates at higher doses (Joiner *et al.*, 2001). Moreover, certain recent studies revealed, at low dose and low dose-rates, a failure to repair double-strand breaks in the DNA (Rothkamm *et al.*, 2003). These phenomena suggest that the cell defense processes against the effects of ionizing radiations are less efficient when the level of exposure is low. Nevertheless, certain authors stated the assumption that this hyper sensitivity at very low dose would involve an elimination of the injured cells and thus, paradoxically, a reduction of the risk of long-term effect.
- Irradiation experiments using micro-beams demonstrated that the target of ionizing radiation is not only the DNA and nucleus, but the whole cell, as a cytoplasmic irradiation may induce mutations with no noticeable effects on the cell survival (Wu *et al.*, 1999).
- The bystander effect demonstrates that the number of cells showing genetic mutations may be higher than the number of cells penetrated by a ionizing radiation. Indeed, various modifications (mutations, gene induction, survival decrease, etc.) were highlighted in non-irradiated cells (Zhou *et al.*, 2000 and 2001; Mothersill and Seymour, 2001; Morgan, 2003a and b). Such genetic alterations would depend on signals generated by the irradiated cells and transmitted by diffusible factors and/or by the pores of inter-cell junctions (Azzam *et al.*, 2003). This phenomenon is to be compared with older observations on clastogenic factors present in the blood of subjects several years after their irradiation, these factors being likely to induce cell genetic modifications.
- The genomic instability observed in the descent of irradiated cells, but also in non-irradiated cells altered by the bystander effect, increases the probability for cancerous conversion (Hoeijmakers, 2001; Huang *et al.*, 2003). The genomic instability results, after various cell divisions following irradiation, in biological alterations (chromosomal modifications, mutations, decrease in cell survival, amplification of genetic material, micro-nuclei, etc.), which are not identical in all cells (Morgan 2003 a and b; Lorimore *et al.*, 1998). It should be noted that this phenomenon would not be the consequence of a mutation but, mainly, of modifications in the genome control and genic expression, functions that would basically be regulated by the cell micro-environment (Baverstock, 2000).
- Furthermore, the risk assessment for the overall population should incorporate the impact of individual radio sensitivity, which intervenes in the capability to repair the DNA lesions, in the adaptive response which could not be evidenced for all individuals being tested. Also, the genetic patrimony might play a part in the radio induced genetic instability (Kadhim, 2003).
- Furthermore, other stochastic effects than those previously described (hereditary effects and cancerous pathologies) were observed on the cohort of Hiroshima and Nagasaki survivors: cardiovascular pathologies, etc. (Preston *et al.*, 2003). These pathologies cannot result from modification to the genetic patrimony in one cell only.

The scientific progresses highlighted an increasing complexity of the phenomena involved. Their mechanisms and their contribution to the carcinogenesis process are still to be specified and steps are still ill-known. In addition, for low dose exposures, certain results suggest a higher effect, other a lower effect than predicted by the linear no threshold relationship, with the existence of a threshold even being possible. It is thus unlikely to be able - in short term - to quantify the carcinogenesis process and thus, to define the form of the dose-effect relationship(s), from fundamental biology data. The only approach remaining valid at present to assess the risk, is the approach applied by the ICRP, which consists in taking the observed effects as a basis.

III.4. Assessment of health consequences through epidemiology

During many years, the epidemiology of ionizing radiation was based on the study of long term effects in the population of the Hiroshima and Nagasaki survivors. This cohort study covering more than 80,000 people presents a sufficient statistical power to study the risk depending on the irradiation dose, and this through a monitoring for more than 40 years. The quality of this study is based on a strict health monitoring (few were dropped out, study of death rate and morbidity conducted in parallel) and a retrospective individual assessment of the exposure, which generated numerous expert surveys worldwide. It remains a unique possibility for studying the cancer risk depending on time since the exposure, on the age at the time of exposure, depending on the type of cancer and its histology at the time of diagnostic and, of course, depending on the dose received in 1945. The uncertainty of this dosimetric assessment was often discussed and it may be considered that the results of this cohort study remain a reliable basis for the radioprotection regulation, in the current state of our knowledge.

However, during the ten past years, a number of studies on other cohorts were implemented and conducted worldwide, in order to check whether the Hiroshima and Nagasaki results could be extrapolated to other populations than the Japanese population (incorporation of co-factors, especially relating to the life style and feeding). The results observed after a flash exposure of some seconds, concerning the whole body, are not systematically identical to the results after an exposure spread over long periods, whether it is an external irradiation, whole body, or internal contamination preferably aimed at a target organ. With regard to internal contamination, the type of radiation involved should be considered and the comparison between a gamma external exposure and an alpha internal exposure requires incorporating the energy deposited on the target cell and a discussion of the weighting factor for the radiation involved.

The results of studies on cohorts of uranium miners who inhaled radon radioactive progeny, generated a number of discussions within the radioprotection committees, because these results did not agree with the predictions obtained from the extrapolation of the Hiroshima and Nagasaki results (using the lung cancer risk coefficient per unit of dose). The discussion mainly concerned the weighting factor 20 for alpha radiation, but it should not be forgotten that this exposure in mining environment, spread over numerous years and resulting from inhaling, may generate biological mechanisms being quite different from a whole body external irradiation, received within some seconds.

At present, the epidemiologic cohort studies also apply statistical models incorporating mechanisms capable of describing the development of an irradiated cell to a cancerous process, whether during the initiation, promotion of cell conversion phase.

Pertinent studies for a better assessment of the risk induced by chronic exposure

For most studies involving a chronic exposure, thus spread over numerous years, the study quality depends on the accuracy of the individual exposure recorded in time, based on a monthly, or yearly, exposure. The final purpose is to test the variation in the health risk depending on the level of the cumulative exposure in time, and to see if the exposure rate may modify the dose-effect relationship. It should be noted that the rate, i.e. the exposure spreading in time, should not be confused with the dose fractionation, notion applied in radiotherapy, as the time scale is quite different.

Studies in occupational environment appear to be the best approach for studying the health risk after a chronic exposure, even if the individual exposure is obviously low.

Studies after a medical exposure may also provide information in this domain, provided they concern individual exposures, well documented and spread over long periods, for example certain chronic diseases, requiring a systematic radiological monitoring, or certain exposures of young children.

The exposure to natural sources of ionizing radiation also allowed in some cases an approach of the risk after internal contamination. Wide case-reference studies allowed studying the lung cancer risk

by reproducing the exposure to domestic radon during the 30 years preceding the cancer diagnostic. These are analytic studies, requiring a deep cooperation of the patients selected as cases and as references; indeed, these people accepted the measurement of their exposure to radon inside their different homes occupied during the past thirty years. In addition, these studies allowed to accurately interrogate on a strong, and sometime simultaneous with exposure to radon, carcinogenic factor: nicotinism. These studies thus allow studying the risk for a chronic exposure over a 30-year period, after adjustment on the tobacco factor. They also allow studying the type of interaction between these two carcinogenic elements by implementing additive or multiplicative models. They will allow comparing the risk models derived from the miner studies with those derived from domestic exposure.

Some authors develop descriptive studies by comparing the health indicators of different regions being more or less exposed to radiation: these studies allow describing the evolution of a health indicator depending on time, on the age, but the demonstration of a causal relationship between an environmental exposure and an average health indicator, observed within a population at a specified time is not conclusive, especially in case of low exposure; too many co-factors may be involved; at the most, such studies may suggest assumptions for future analytic studies.

It is possible to use geographic studies facing a strong carcinogenic factor, or facing a very rare disease whose incidence dramatically increases. These studies are used for alert purposes and require the subsequent development of analytic studies like, for example, the detection of a high rate of thyroid cancers for young children in Belarus and in Ukraine after the Chernobyl accident.

As a conclusion, the studies of health effects induced by chronic exposures are currently part of a wide research field in which the part of epidemiology is important; the knowledge of underlying biological mechanisms would provide a real help in the interpretation of results obtained from varied populations and exposures. The selection of studies highly depends on the quality of individual dosimetry and on the possibility to conduct large scale studies.

IV. Conclusions and IRSN recommendations

The phenomena concerning internal contamination by radionuclides are complex because they involve numerous physico-chemical, biochemical and physiological mechanisms, still ill-known and thus difficult to model. Due to this complexity, the behaviour of radionuclides in the organism is often ill described and it is difficult to accurately define a relationship between the dose delivered by radionuclides and the observed consequences on health. This led the radioprotection specialists to mostly use the dose/risk relationships derived from the study of the Hiroshima/Nagasaki survivors, exposed in conditions very different from those met in the cases of internal contaminations.

This fact raises numerous questions, which should be considered with caution because a wide part of the public exposure in some areas of the world is due to chronic internal contaminations and very few data concern these situations.

The ECRR attempted to solve these gaps by proposing to modify the ICRP radioprotection system and to arbitrarily decrease the annual exposure limits. Although the questions raised by the ECRR are fully acceptable, the fact is that the arguments stated to justify this doctrine modification are not convincing, as the demonstration as a whole does not meet the criteria of a strict and consistent scientific approach.

The basic question is to know whether the radioprotection system currently applied, which states to be conservative, designed to cover a large number of situations, protects or not the populations exposed by internal contamination, with a sufficient margin of safety. The latest works aiming at comparing the risk coefficients calculated from studies conducted on individuals exposed to radon-222, thorium-232, radium isotopes and plutonium-239, with those predicted by the current Hiroshima/Nagasaki model, appear to be heartening on this question as they demonstrate that the current model would in fact tend to slightly over-estimate the risk for certain cancers⁸ to occur after

⁸ *Leukemias and bone cancers*

an internal contamination by alpha emitters (Harrison and Muirhead, 2003). On the other hand, these works do not cover all radionuclides that may induce health problems, especially certain fission products found on some industrial sites (e.g. ^{90}Sr) or certain other beta emitters or Auger electrons. Furthermore, the whole scientific community now recognizes that the assessments of risks induced by internal contaminations are affected by uncertainties and that the concept of risk is difficult to use. The CERRIE committee, in charge of studying these risks, concluded in its report that, whenever possible, the assessments of doses and risks should be provided with an explicit description of the associated uncertainties (CERRIE, 2004). In addition to these recommendations, the Committee Chairman concludes that "*the uncertainties in the internal radiation risks can be large and these need to be taken properly into account in policy and regulatory decisions*" (Goodhead, 2004).

The major problem is that, if these uncertainties are acknowledged, they are difficult to quantify and we do not possess, in the current state of knowledge, the elements required to improve the existing radioprotection system. The IRSN thus considers that the structure and bases of this system should not be modified for the time being, because it corresponds to the best tool being available at present for protecting human from the deleterious effects of ionizing radiations. However, some elements of the system might be improved by integrating in a more explicit and systematic way uncertainties related to the determination of the dose after internal contamination.

A significant improvement of the radioprotection system in the field of internal contamination can be conceivable only by development of studies and research. IRSN recommends therefore to initiate researches in some specific fields in order to acquire missing knowledge and to better quantify uncertainties associated with the estimate of risks consecutive to internal chronic contaminations.

IRSN recommends first to initiate researches in order to respond to the questions of populations living in the Eastern Europe contaminated territories. The fears of these populations are due to the observation of cardiovascular pathologies, decreasing birth rates and behavior troubles, which would directly be due to the Chernobyl accident, according to some scientists. The problem lies in the absence of reliable data to determine at present if a direct causation exists between the internal contamination level of these populations and these pathologies. Consequently, the IRSN considers that it is urgent to initiate specific researches in this area in order to provide initial response elements.

The IRSN then recommends then to initiate in-depth researches in order to improve the knowledge in the area of health consequences of chronic internal contaminations and to reduce the related uncertainties.

- Researches should first cover the kinetics of radionuclides in the organism after a chronic exposure, in order to accurately determine the location and time of residence of the elements. The purpose of these researches will be to check whether the accumulation and excretion kinetics are sensitive or not to the exposure duration. Researches should first of all be conducted on known radionuclides to focus on certain tissue or cell structures (uranium, transuranic elements, strontium, etc.), because these interactions with living matter may be modified during long term exposures. Kinetic data are essential to determine the dose delivered to the tissues and to the whole organism and will be used as basic data when determining risk coefficients.
- Researches should then concern the toxicity of radionuclides, not only focusing to cancers but also to the other types of effects and to all tissues. The main criticism to the current system is that it is mainly based on the detriment notion, itself relating to the probability for a cancer or severe hereditary effects to occur. At present, this detriment does not incorporate other pathologies and, in fact, researches conducted during the past years in radiotoxicology basically focused to the occurrence of cancers while neglecting other effects. It is now important to fill the gaps in this area and to describe all biological and health effects that may occur after a chronic contamination by radionuclides.
- Finally, most studies discussed in the ECRR report were limited to descriptive studies, comparing incidence rates for different environmental contamination levels. Facing chronic exposures, varying in time and with a non homogeneous distribution within the populations considered, the so-called descriptive or ecological studies have few chances to highlight a

risk, especially a risk for cancer developing after a long latency time. Consequently, the IRSN recommends to increase the analytic epidemiologic studies aiming at a better assessment of the cancer risk depending on the dose on the target organ. A suitable effort should be made to successfully conduct the new studies that will be initiated soon on other cohorts of workers in Europe, more especially exposed to certain radionuclides like uranium. The purpose of these studies is to target populations whose internal exposure was correctly assessed, to monitor them over more than 20 years, and to record a set of health indicators (cancers, leukemias, chronic kidney, lung, cardiovascular troubles...). These studies will be conducted within the scope of a program supported by the European Union. In final, they will provide additional knowledge on the risks induced by low dose internal exposures.

All these studies will allow a better understanding of the internal contamination phenomena and their consequences on health. They will provide the basic data that are failing in this area and will thus contribute to improve our whole radioprotection system. However, these researches require an effort supported for many years and a very developed and diversified technical platforms, implying a pooling of considerable human means. These researches should thus be undertaken within an international framework in the form of joint actions at the European or World level.

References

- AZZAM E.I., DE TOLEDO S.M., LITTLE J.B. Oxidative metabolism, gap junctions and the ionizing radiation-induced bystander effect. *Oncogene* 22(45), 7050-7057, 2003.
- BANDAZHEVSKY, Yu.I. *Pathology of incorporated radioactive emission*. Gomel State Medical Institute. Minsk, 2001.
- BARCELLOS-HOFF M.H. It takes a tissue to make a tumor: epigenetics, cancer and the microenvironment. *J. Mammary Gland Biol. Neoplasia* 6(2), 213-221, 2001.
- BARHHART B.J. and COX S.H. Mutagenicity and cytotoxicity of 4.4-MeV alpha particles emitted by plutonium-238. *Radiat. Res.* 80, 542-548, 1979.
- BAVERSTOCK K. Radiation-induced genomic instability: a paradigm-breaking phenomenon and its relevance to environmentally induced cancer. *Mutat. Res.* 454(1-2), 89-109, 2000.
- BENSON J.M., CHANG I.Y., CHENG Y.S., HAHN F.F., and SNIPES M.B. "Effects of repeated inhalation exposure of F344 rats and B6C3F1 mice to nickel oxide and nickel sulfate hexahydrate on lung clearance." *LRRR report*, 1992.
- BOULHADOUR H., PAQUET F. and NÉNOT, J.C. Neptunium. In: *Toxiques Nucléaires* (Ed. P.Galle). Masson, Paris, 1997.
- CERI Etude des effets sanitaires de l'exposition aux faibles doses de radiation ionisante à des fins de radioprotection. Recommandations 2003 du Comité Européen sur le Risque de l'Irradiation. Edition Frison Roche, 2003.
- CERRIE Report produced by the Committee Examining Radiation Risks of Internal Emitters, London. 31 pp., 2004.
- CERUTI R, GHISLENI G, FERRETTI E, CAMMARATA S, SONZOGNI O, SCANZIANI E. Wild rats as monitors of environmental lead contamination in the urban area of Milan, Italy. *Environ Pollut.* 117, 255-259, 2002.
- CHARLES M.W., MILL A.J. and DARLEY P.J. Carcinogenic risk of hot-particle exposures. *J. Radiol. Prot.* 23, 1-3, 2003.
- CHEN D.J., STRNISTE G.F. and TOKITA, N. The genotoxicity of alpha particles in human embryonic skin fibroblasts. *Radiat. Res.* 100, 321-327, 1984.
- COLLIS S.J., SCHAWINGER J.M., NTAMBI A.J., KELLER T.W., NELSON W.G., DILLEHAY L.E. and DE WEESENTL Evasion of early cellular response mechanisms following low level radiation-induced DNA damage. *J. Biol. Chem.* 279(48), 49624-32, 2004
- DURBIN P.W., KULLGREN B., XU J. and RAYMOND K.N. New agents for in vivo chelation of uranium(VI): efficacy and toxicity in mice of multidentate catecholate and hydroxypyridinonate ligands. *Health Physics* 72, 865-879, 1997.
- GALLE, P. Uranium. In: *Toxiques Nucléaires* (Ed. P.Galle). Masson, Paris, 1997.
- GOODHEAD D. Committee Examining Radiation Risks of Internal Emitters. Press Release, Wednesday 20th October 2004, 11.00 am. 2004
- HANAHAN D., WEINBERG R.A. The hallmarks of cancer. *Cell* 100(1), 57-70, 2000
- HARRISON J.D. and MUIRHEAD C.R. Quantitative comparisons of cancer induction in humans by internally deposited radionuclides and external radiation. *Int. J. Radiat. Biol.* 79, 1-13, 2003.

- HOEIJMAKERS J.H. Genome maintenance mechanisms for preventing cancer. *Nature* 411(6835), 366-374, 2001.
- HUANG L., SNYDER A.R., MORGAN W.F. Radiation-induced genomic instability and its implications for radiation carcinogenesis. *Oncogene* 22(37), 5848-5854, 2003.
- ICRP. *Age-Dependant Doses to Members of the Public From Intakes of Radionuclides. ICRP Publication 56. Part 1.* Pergamon Press, Oxford. 1989
- ICRP. *Recommendations of the International Commission on Radiological Protection. ICRP Publication 60.* Pergamon Press, Oxford. 1990
- ICRP. *Protection of the Public in Situations of Prolonged Radiation Exposure. ICRP Publication 82.* Elsevier Science Ltd, London. 1999
- ICRP. *Relative Biological Effectiveness (RBE), Quality Factor (Q) and Radiation Weighting Factor (WR).* ICRP Publication 92. Elsevier Science Ltd, London. 2003
- ICRP. *Recommendations of the International Commission on Radiological Protection.* ICRP Publication 60, Elsevier Science Ltd. Oxford. 1990
- ICRP. *Age-dependant doses to members of the public from intakes of radionuclides : Part 2, ingestion dose coefficients.* ICRP Publication 67. Elsevier Science Ltd. Oxford. 1993
- ICRP. *Age-dependant dose to members of the public from intakes of radionuclides : Part 3, Ingestion dose coefficients.* ICRP Publication 69. Elsevier Science Ltd. Oxford. 1995
- ICRP. *Individual monitoring for internal exposure of workers.* ICRP Publication 78. Elsevier Science Ltd. Oxford. 1997
- ICRP. 1999. *Protection of the public in situations of prolonged radiation exposure.* ICRP Publication 82. Elsevier Science Ltd. Oxford.
- JOINER M.C., MARPLES B., LAMBIN P., SHORT S.C., TURESSON I. Low-dose hypersensitivity: current status and possible mechanisms. *Int. J. Radiat. Oncol. Biol. Phys.* 49(2), 379-89, 2001.
- KADHIM M.A. Role of genetic background in induced instability. *Oncogene* 22(45), 6994-6999, 2003.
- KASSIS AI, HAVELL RW, SASTRY KSR, ADELSTEIN SJ. Positional effects of Auger decays in mammalian cells in culture. In: *DNA damage By Auger emitters.* BAVERSTOCK, K.F. CHARLTON, D.E. (Eds), Taylor and Francis. London 1-13; 1988.
- KEMPF H. *La faute de Youri Bandhazevski.* Le Monde 24 Juin 2003
- KRTOLICA A., CAMPISI J. Cancer and aging: a model for the cancer promoting effects of the aging stroma. *Int. J. Biochem. Cell Biol.* 34(11), 1401-1014, 2002
- LANG S., KOSMA V.M., SERVOMAA K., RUUSKANEN J. & RYTOMAA T. Tumour induction in mouse epidermal cells irradiated by hot particles. *Int. J. Radiat. Biol* 63, 375-381, 1993.
- LEGGETT R.W., ECKERMAN K.F., and WILLIAMS L.R. Strontium-90 in bone : a case study in age dependant dosimetric modeling. *Health Physics* 43, 307-322, 1982.
- LIKHTAREV I.A., REPIN V.S., BONDARENKO O.A. and NECHAEV S.Y. Radiological effects after inhalation of highly radioactive fuel particles produced by the Chernobyl accident. *Radiat. Prot. Dos.* 59, 247-254, 1995.
- LLOYD R.D., TAYLOR G.N., MILLER S.C., BRUENGER F.W. AND JEE W.S.. Review of 239Pu and 226Ra effects in beagles. *Health Physics* 81, 691-697, 2001.

- LORIMORE S.A., KADHIM M.A., POCOCK D.A., PAPWORTH D., STEVENS D.L., GOODHEAD D.T., WRIGHT E.G. Chromosomal instability in the descendants of unirradiated surviving cells after alpha-particle irradiation. *Proc. Natl. Acad. Sci. USA* 95(10), 5730-5733, 1998.
- MIRTO H., HENGE-NAPOLI M.H., GIBERT R., ANSOBORLO E., FOURNIER M. & CAMBAR J. Intracellular behaviour of uranium(VI) on renal epithelial cell in culture (LLC-PK1): influence of uranium speciation. *Toxicol. Lett.* 104, 249-256, 1999.
- MORGAN W.F. Non-targeted and delayed effects of exposure to ionizing radiation: I. Radiation-induced genomic instability and bystander effects in vitro. *Radiat Res.*, 159(5), 567-80, 2003.
- MORGAN W.F. Non-targeted and delayed effects of exposure to ionizing radiation: II. Radiation-induced genomic instability and bystander effects in vivo, clastogenic factors and transgenerational effects. *Radiat. Res.* ;159(5), 581-96, 2003.
- MOTHERSILL C., SEYMOUR C. Radiation-induced bystander effects: past history and future directions. *Radiat. Res.* 155(6), 759-67, 2001.
- PAQUET F., RAMOUNET B., METIVIER H. AND TAYLOR D.M. The effect of the mass and initial chemical form of neptunium on its molecular associations in blood and liver. *Radiat. Res.* 146, 306-312, 1996.
- PARK C.C., BISSELL M.J., BARCELLOS-HOFF M.H. The influence of the microenvironment on the malignant phenotype. *Mol. Med. Today* 6(8), 324-329, 2000.
- PRESTON D.L., SHIMIZU Y., PIERCE D.A., SUYAMA A., MABUCHI K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat. Res.* 160(4), 381-407, 2003.
- RENAUD-SALIS V., LATAILLADE G., and MÉTIVIER H.. "Effect of mass, oxidation state and duration of chronic ingestion on plutonium absorption in fed rats." *Int. J. Radiat. Biol.* 58, 691-704, 1990.
- RIGAUD O., MOUSTACCHI E. Radioadaptation for gene mutation and the possible molecular mechanisms of the adaptive response. *Mutat. Res.* 358(2), 127-134, 1996.
- RIGAUD O. The adaptive response to ionizing radiation: low dose effects unpredictable from high dose experiments. *Hum. Exp. Toxicol.* 18(7), 443-6, 1999.
- ROTHKAMM K., LOBRICH M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. *Proc. Natl. Acad. Sci. USA* 100(9), 5057-5062, 2003.
- SCWHARTZ J.L., ROTMENSCH J., ATCHER R.J., JOSTES R.F., CROSS F.T., HUI T.E., CHEN D., CARPENTER S., EVANS H.H. and MENCL J. Interlaboratory comparison of different alpha-particle and radon sources: cell survival and relative biological effectiveness. *Health Physics* 62, 458-461, 1992.
- SERVOMAA K. and RYTOMAA T. Malignant transformation of mouse fibroblasts by uranium aerosols released from Chernobyl. In: *Frontiers in Radiation Biology* (Ed. E. Riklis). VCI, Weinheim, 1990.
- SHAGINA N.B., TOLSTYKH E.I., ZALYAPIN V.I., DEGETEVA M.O., KOZHEUROV V.P., TOKAREVA E.E., ANSPAUGH L.R. and NAPIER B.A.. Evaluation of age and gender dependences of the rate of strontium elimination 25-45 years after intake : analysis of data from residents living along the Techa river. *Radiat. Res.* 159, 239-246, 2003.
- SIGG M., CROMPTON N.E. and BURKART W. Enhanced neoplastic transformation in an inhomogeneous radiation field: an effect of the presence of heavily damaged cells. *Radiat. Res.* 148, 543-547, 1997.

- TAULAN M. *Conséquences moléculaires d'une contamination aiguë et chronique à l'uranium : étude du transcriptome murin*. Thèse de doctorat de l'université de Montpellier, 2004. 118 pp. Rapport IRSN 2004/44-FR.
- THACKER J., STRETCH A. and GOODHEAD D.T. The mutagenicity of alpha particles from plutonium-238. *Radiat. Res.* 92, 343-352. 1982
- UNSCEAR. *Sources and effects of ionizing radiations*. United Nations Scientific Committee on the Effects of Atomic Radiation, 1994 Report to the general assembly, UN, New York. 1994
- UNSCEAR. *Sources and effects of ionizing radiation*. Volume II. United Nations Scientific Committee on the Effects of Atomic Radiation, 2000 Report to the general assembly, UN, New York. 2000
- WHO. *Environmental health criteria 6. Principles and methods for evaluating the toxicity of chemicals. Part I* : Published under the joint sponsorship of the United Nations Environment Programme and the World Health Organization. WHO, Geneva, 1978. pp. 272. ISBN 92 4 154066 4. 1978
- WU L.J., RANDERS-PEHRSON G., XU A., WALDREN C.A., GEARD C.R., YU Z., HEI T.K.. Targeted cytoplasmic irradiation with alpha particles induces mutations in mammalian cells. *Proc. Natl. Acad. Sci. USA* 96(9), 4959-64, 1999.
- ZAMORA M.L., TRACY B.L., ZIELINSKI J.M., MEYERHOF D.P., and MOSS M.A. Chronic ingestion of uranium in drinking water: a study of kidney bioeffects in humans. *Toxicol. Sci.* 43, 68-77, 1998.
- ZHOU H., RANDERS-PEHRSON G., WALDREN C.A., VANNAIS D., HALL E.J., HEI T.K. Induction of a bystander mutagenic effect of alpha particles in mammalian cells. *Proc. Natl. Acad. Sci. USA* 97(5), 2099-104, 2000.
- ZHOU H., SUZUKI M., RANDERS-PEHRSON G., VANNAIS D., CHEN G., TROSKO J.E., WALDREN C.A., HEI T.K. Radiation risk to low fluences of alpha particles may be greater than we thought. *Proc. Natl. Acad. Sci. USA* 98(25), 14410-5, 2001.