The health effects of low-dose ionizing radiation

New epidemiological results and perspectives

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The evaluation of the health effects of low-dose ionizing radiation has always been a focus of controversy. At first sight, this seems paradoxical since the epidemiological data of Hiroshima-Nagasaki and decades of radiobiological research have yielded considerable knowledge of the potential health impacts. This article explores how current risk management in the nuclear industry are trying to factor uncertainties into a precautionary approach.

The cancer hazard of ionizing radiation has been characterized by the International Agency for Research on Cancer (IARC) and the World Health Organisation (WHO), since epidemiological evidence first came available. As a result, many social security systems have taken ionizing radiation into consideration for compensation as an occupational disease, at least if evidence of attribution or poor protective practice can be shown, but also for preventive measures for pregnant workers.

This article looks at the relative risk of low level exposure to ionizing radiation, as it occurs in the environment, at the workplace and in patient exposure excluding cancer therapy (where radiation is used to kill off malignant cells).

We first consider the nature of the effects distinguishing between stochastic and non stochastic effects (defined below). The biological mechanisms of interaction with radiation are highlighted. We endeavour to explain the reasons for the controversy, perceptual differences, group dynamics and interests. We then discuss the findings of recent epidemiological studies and some prospects offered by new scientific insights in molecular biology, focusing on ethics and occupational diseases. Particular attention is paid to increased foetal exposure risks. We conclude with a look at the multifactorial exposure challenge.

Biological Effects of Ionizing Radiation

There is no question about the health effects of high-dose radiation, for which a clear dose-response relationship exists. In these so called deterministic effects, the severity of the effect is directly related to the number of damaged cells. High dose events are exceptional, essentially related to accidents, military action, or medical treatment in which the expected detrimental effect is targeted to eliminate a tumour. Radiation protection policy should prevent any high-dose occupational exposure.

The big concern with low dose exposure is the increased risk of cancer from the increased radiation dose. At low doses, the probability of an effect, but not the severity of the effect, is dose-related. Whatever the low dose received, if a cancer develops, the severity of the effect (resulting in a fatal outcome in half of the cases) is not in question. What must be evaluated, therefore, is the cancer incidence probability. Such delayed effects are called probabilistic or stochastic.

There is no proof of an increased incidence of cancer and other harmful effects of ionizing radiation in humans at doses below 20 millisievert (mSv, see box p. 19), the annual limit for workers, and a dose that can occur in medical radiological examination. Some estimates put this figure much higher, up to 200 mSv, while others consider levels up to 10 mSv of significance for foetal exposure. This lack of evidence could point either to there being no harmful effect at such low levels of radiation, or that whatever health effects may occur are too few to be statistically significant.

The indicator of risk for health, the effective dose, however is an effective tool for many applications, but too indirect and limited in scope for environmental stress and patient exposure in radiology, where considerable limitations of the concept have been identified. Sensitive biological indicators of effects are being developed, but biological effects are not necessary indications of health effects.

Ionizing radiation as emitted by radioactivity is nothing other than a transfer of sufficient energy to a target atom for expelling one electron out of its orbital layer thereby creating an ionization event. The target of the radiation is always an atom. The atoms ionized are those most present in biological systems, like hydrogen and oxygen. The main target, by the law of probability, is the water molecule which represents about 80% of body weight. When water is irradiated, it is dissociated and converted into free radicals (Reactive Oxygen Species, ROS). This process is called water radiolysis. Radicals are highly reactive and give off their energy to their surroundings and damage other molecules, and ultimately DNA, the molecule that carries our genetic information.

DNA makes up only 1% of the total cellular mass and is therefore not highly susceptible of a direct radiation hit. This molecule is critical for cell life and any direct or indirect damage, if not adequately repaired, will have dramatic consequences.

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However, powerful and reliable biological cell control and DNA repair mechanisms exist. Un- or mis-repaired DNA induces an active genetic process that seeks to protect the organism by eliminating the cell through programmed cell suicide, called apoptosis. As a result, only cells that escape such biological controls and apoptosis can become transformed (cancerous).

In more than 80% of cases, the ionizing radiation effect comes down to damage by free radicals. Any other cause that produces free radicals – such as UV and active chemical agents like dioxins – will produce essentially the same biological effect as ionizing radiation.

DNA carries genetic information, and any DNA damage to a somatic cell, if not repaired, can be transmitted to the daughter cells. There are evidences that cellular responses can include genetic change because they can continue to occur (genetic instability) for longer periods over many cell generations. If the damage is caused to germinal cells, the possibility of genetic effects being passed on to unborn children must be considered. Currently available data indicate that the number of expected genetic effects after chronic exposure to 1 unit of Gray (Gy) is about 3000 to 4700 per million births. This is about 0.4 to 0.6% of the natural incidence of genetic effects. Over a lifetime, we in Belgium receive on average a fourth of this dose from medical diagnostic and natural exposure. The International Commission on Radiological Protection (ICRP) considers that thresholds exist for induced malformation during organogenesis, and also that there is no significant risk of IQ impact up to the lower tens of mGy exposure. Foetal effects are not taken into account during the pre-implant (earliest) period of pregnancy. Recent animal studies on both chemical and radiation exposure of genetically predisposed cases show that congenital malformations can occur due to mis-repaired DNA-damaged cells. They do not necessary lead to spontaneous abortion. Considerable uncertainty continues to surround the foetal effects and later cancer proneness associated with radiation induced genetic susceptibility.

The number of illnesses in which genetic factors play a role is high. Numerous studies show that radiosensitivity is linked to cancer proneness that depends on the individual genetic history. Radiation could trigger genetic susceptibility. Molecular biology allows analysis of the integrity of the DNA repair system that includes genes involved in recognizing and signalling the presence of injury and genes controlling a stop process of cellular division in case of DNA damage. This could enable radiosensitivity in individuals to be identified. Repair genes play an important role in cancer processes. The development of tests on their inability as gate-keeping cancer processes could enable higher-risk individuals to be identified.

Meanwhile, the ICRP focuses only on protection for the average man, ignoring individuals with a possible genetic susceptibility by ignoring precaution.

The regulation of low-dose risks and the social debate

Against such a background of increasing knowledge, scientific controversies normally remain on an academic plane. But estimation of the low-dose cancer risk where no evidence of effect can be proved remains the focus of debate and division between and among experts and action groups. At low doses, the risk is essentially estimated by extrapolation of the dose-effect curve obtained from high doses. This Linear No Threshold (LNT) model hypothesizes that risk decreases with dose on the precautionary assumption that any exposure may cause some risk. This has lead to the development of a consistent radiation protection philosophy: nuclear practices are only allowed if justified, and once justified or authorized, protection has to be optimized respecting dose limits as boundary conditions.

The advantage of such an approach is that a proven carcinogen is not black-listed but conditionally allowed for its numerous benefits for society, in particular in medicine.

When cancer is suspected as a potential effect, and when a risk estimation is needed for communication to a broader public, perception plays a key role for the lay person and experts alike. Perceptions differ among experts as much as the public and are influenced by distributive justice, interests and trust. This complicates communication with the public and development of expert approaches. Media focuses and diverging political views create defensive attitudes which can be explained by social theories on cognitive dissonance. Moreover, considerable interests are at play in the nuclear field – both in the energy and medical sectors – which add an economic value to low-dose effects (Eggermont, 2003).

Risk studies indicate that radiation is not highly carcinogenic compared to smoking and asbestos, and risk perception studies show no general public fear of radiation (Hardeman and Carlé, 2003). There is almost no concern about the quite high doses from medical applications or man-enhanced natural exposure (Vanmarcke *et al.*, 2004). By contrast, there is real concern about small, almost virtual long-term future industrial risks, such as from nuclear waste disposal. There is more tolerance of a potentially hazardous technology that delivers benefits than an imposed industrial hazard. This is also illustrated by the differing perceptions of microwave radiation risks from mobile phones compared to mobile phone masts.

The LNT model makes no claim to account for the full scientific complexity, but is a fairly simple tool for operational use. The implementation of present regulations is creating no major problems in a field where simplicity, stability and consistency are demanded.

Recent epidemiological results clarify the issue and support the LNT hypothesis

Recent advances in molecular biology will do much to dispel uncertainties in future, but their application could give rise to ethical issues if genetic susceptibility of individuals to ionizing radiation is demonstrated at the workplace. Biomarkers are specific measurements of an interaction between a biological system and an environmental agent, indicating either exposure, effect or susceptibility.

For most international scientific experts, as represented at UN level, the LNT model remains the best fit to data and its associated uncertainties; it is a kind of precautionary rationality and a common sense choice. The polarization of opinions between believers and non-believers in low-dose effects overshadows peer reviewed scientific references at international level, as represented by UNSCEAR, NAS and BEIR[1].

The French academy and some professional medical organizations are fiercely opposed (Tubiana *et al.*, 2005) to the fundamentals of existing regulations, while scientists with opposing views have organized themselves in an international network (ECRR)[2] claiming that high risks exist even at low doses. Worker exposure to ionizing radiation is a big issue in the medical sector and air flight companies while environmental issues are predominant in the nuclear power industry.

The clear-up costs of former military contaminations featured in the US Congress debates on low-dose risks: setting a threshold could help to minimize costs, and this could also benefit the decommissioning of civil nuclear power plants in future.

The French academy seems more concerned that new technological developments in medicine should not be held back by low-dose concerns. On the other hand, however, they are faced with high deterministic doses for patients and medical staff in new practices like interventional radiology, where optimization based on LNT could help. From LNT comes the ALARA (As Low As Reasonably Achievable) principle, today a basis of radiation protection. We would argue that this policy has proved its usefulness and success, and should be kept as long as no reliable scientific evidence impels a change. Especially so as the policy can be considered as a precautionary approach.

New epidemiological evidence supports the LNT hypothesis

International epidemiological research on the health effects of low-dose ionizing radiation has advanced in a textbook way through dose estimations of exposed populations. Two studies were recently published, one by the UN WHO International Agency on Research on Cancer (IARC) (Cardis *et al.*, 2005) and an EU initiative on the effects of exposure to indoor radon (Darby *et al.*, 2004).

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the ICRP and the US National Academy of Sciences (BEIR VII) reviewed scientific progress worldwide, and recently came to conclusions that still support a linear non-threshold hypothesis as the best fit to assess and manage low level exposure to ionizing radiation in the current context of uncertainty.

This international peer review of the science, however, is taken issue with both by the French Academy of Sciences, which dismisses low-dose effects, and by a new international network of scientists which postulate increased effects at low doses (ECRR).

What do recent epidemiological findings teach us? The IARC conducted a collaborative study of more than 400 000 nuclear industry workers worldwide with past exposure to ionizing radiation (see table p. 24). This cohort study was carried out in 15 countries to further improve the precision of direct estimates of risk after protracted low dose exposures and to strengthen the scientific basis of radiation protection. It presents risk estimates for mortality from all cancers, excluding leukaemia, and from leukaemia excluding chronic lymphocytic leukaemia and compare them with estimates derived from data on survivors of the A bomb.

The exposed group essentially comprises men (90%) while recent data on radiation-induced thyroid cancer shows a higher risk for women, especially for those exposed during childhood. The mean cumulated dose of the worker cohort was low, only 19.4 mSv; 90% received doses below the former occupational dose limit of 50 mSv.

The IARC study is a major scientific complement to the still ongoing follow-up of the Hiroshima-Nagasaki data on bomb survivors. The results as summarized in the *British Medical Journal* are as follows (Cardis *et al.*, 2005): "The excess relative risk for cancer other than leukaemia and from leukaemia was 0.97 per Sv, 95% confidence interval 0.14 to 1.97. Analyses of causes of death related or unrelated to smoking indicate that, although confounding by smoking may be present, it is unlikely to explain all of this increased risk. The excess relative risk for leukaemia excluding chronic lymphocytic leukaemia was 1.93 per Sv (< 0 to 8.47). On the bases of these estimates, 1-2% of deaths from cancer among workers in this cohort may be attributable to radiation."

These estimates, from the largest study of nuclear workers ever conducted, are higher than, but statistically

[1] UNSCEAR: United Nations Scientific Committee on Effects of Atomic (Ionizing) Radiation; NAS: National Academy Sciences, USA; BEIR: Biological Effects Ionizing Radiation, USA. See: www.nap.edu/books/030909156X/html.

[2] European Committee on Radiation Risks; see: www.euradcom.org.

Risk of cancer after low doses of ionizing radiation: retrospective cohort study in 15 countries

						Deaths				
	No. of facilities	First year of operations	Follow-up period	No. of workers	Person / years	All causes	All cancers excluding leukaemia	Leukaemia excluding CLL	Collective cumulative dose (Sv)	Average individual cumulative dose (mSv)
Australia	1	1959	1972 - 1998	877	12,110	56	17	0	5.4	6.1
Belgium	5	1953	1969 - 1994	5,037	77,246	322	87	3	134.2	26.6
Canada	4	1944	1956 - 1994	38,736	473,880	1,204	400	11	754.3	19.5
Finland	3	1960	1971 - 1997	6,782	90,517	317	33	0	53.2	7.8
France CEA-COGEMA	9	1946	1968 - 1994	14,796	224,370	645	218	7	55.6	3.8
France EDF	22	1956	1968 - 1994	21,510	241,391	371	113	4	340.2	15.8
Hungary	1	1982	1985 - 1998	3,322	40,557	104	39	1	17.0	5.1
Japan	33*	1957	1986 - 1992	83,740	385,521	1,091	413	19	1,526.7	18.2
Korea (south)	4	1977	1992 - 1997	7,892	36,227	58	21	0	122.3	15.5
Lithuania	1	1984	1984 - 2000	4,429	38,458	102	24	1	180.2	40.7
Slovak Republic	1	1973	1973 - 1993	1,590	15,997	35	10	0	29.9	18.8
Spain	10	1968	1970 - 1996	3,633	46,358	68	25	0	92.7	25.5
Sweden	6	1954	1954 - 1996	16,347	220,501	669	190	4	291.8	17.9
Switzerland	4	1957	1969 - 1995	1,785	22,051	66	24	0	111.2	62.3
UK	32	1946	1955 - 1992	87,322	1,370,101	7,983	2,201	54	1,810.1	20.7
US - Hanford	1	1944	1944 - 1986	29,332	678,833	5,564	1,279	35	695.4	23.7
US - INEL	1	1949	1960 - 1996	25,570	505,236	3,491	886	26	254.6	10.0
US - NPP	15	1960	1979 - 1997	49,346	576,682	983	314	19	1336.0	27.1
US - ORNL	1	1943	1943 - 1984	5,345	136,673	1,029	225	12	81.1	15.2
TOTAL	**154**	**-**	**-**	**407,391**	**5,192,710**	**24,158**	**6,519**	**196**	**7,892.0**	**19.4**

CEA-COGEMA: Commissariat à l'Energie Atomique – Compagnie Générale des Matières Nucléaires; **EDF:** Electricité de France; **NPP:** Nuclear Power Plants; **INEL:** Idaho National Engineering Laboratory; **ORNL:** Oak Ridge National Laboratory; **CLL:** Chronic Lymphocytic Leukaemia.
* No information available to allow separation of different facilities.

Source: Cardis, E., *et al.*, 2005

compatible with, the risk estimates used for current radiation protection standards. The results suggest that there is a small excess risk of cancer, even at the low doses and dose rates typically received by nuclear workers in this study.

The confounding effect of smoking was considered in first approximation, yielding only a significant higher risk for lung cancer (ERRor: 0.3 - 4.0 / Sv)[3]. The relevance of this study is that it confirms the LNT hypothesis, with a broad confidence level, except for leukaemia where a quadratic hypothesis was already made. For solid tumours, mortality was estimated two to three times higher than the linear hypothesis from the Hiroshima-Nagasaki data, yielding a 1-2% attribution of cancer deaths to ionizing radiation, which remains a low risk compared to that of some other carcinogens.

The second set of epidemiological data concerns indoor exposure to radon. After earlier epidemiological studies on miners, the more recent case control studies of radon-induced lung cancer in the home were analysed together in the EU, and in the USA and China.

The results for the EU were: "The mean measured radon concentration in homes in the control group was 97 Bq/m^3... For cases of lung cancer the mean concentration was 104 Bq/m^3. The risk of lung cancer increased by 8.4% (95% confidence interval 3.0% to 15.8%) per 100 Bq/m^3 increase in measured radon (P=0.0007)... The dose-response relation seemed to be linear with no threshold and remained significant (P=0.04) in analyses limited to individuals from homes with measured radon < 200 Bq/m^3... In the absence of other causes of death, the absolute risks of lung cancer by age 75 years at usual radon concentrations of 0, 100, and 400 Bq/m^3 would be about 0.4%, 0.5% and 0.7%, respectively, for lifelong non-smokers, and about 25 times greater (10%, 12% and 16%) for cigarette smokers."

Collectively, though not separately, these studies show appreciable hazards from residential radon, particularly for smokers and recent ex-smokers, and indicate that radon is responsible for about 2% of all deaths from cancer in Europe.

The EU collaborative analysis yields a risk estimation of this indoor environmental exposure of 20 000

[3] More than 5 000 cases of thyroid cancer have been identified in young people in the environs of Chernobyl to date, mostly exposed to high doses (~ 1 Gy), but with a lower-than-expected mortality.

lung cancers a year in Europe. This means that 2% of the total number of cancers in Europe could be radon-related, but with a broad margin of uncertainty. Again, the results indicate that effects could occur at relatively low concentrations, frequently found in Europe from 100 Bq/m³ on, corresponding to a dose of 2-3 mSv/y, and support linearity as the most plausible model, and that at lower levels than previously suggested.

Multi-factorial exposure and ethical concerns

Smoking was a confounding factor in both studies. Simultaneous exposure to different agents at work or in the environment is a daily reality which complicates the study of the effects of these agents. Synergistic effects were already demonstrated in uranium miners and also with UV exposure.

A bigger focus should be placed on multi-causality in risk assessment and management. It could have considerable implications for the evaluation of scientific evidence of hazards. This was recently argued by the Director of the European Environment Agency (EEA): "Multi-causalities could cause a kind of network perturbation generated by small, almost imperceptible, changes in lots of genes. The removal of small environmental co-causal factors can have a real sense not only for cancer, but as already clearly demonstrated, for diseases like asthma" (McGlade, 2005).

The difficulties of exposure assessment as discussed above for radiation exposure could be overcome with new technological opportunities to identify genes interacting in disease processes. The causes of a common disease like cancer seem to be the result of dependent actions of multiple agents. The revival of a co-causal or interaction factor could have substantial beneficial effects in prevention. Therefore it recently became a priority for the EEA.

In this context, the focus should shift from attributing probability of causation to individual factors to developing a more precautionary approach towards our present uncertainties and lack of knowledge.

Epidemiology was the historical reference for risk assessment and management in identifying hazardous factors and the risks of exposure to them. It will continue to play a dominant role if subjected to methodological scrutiny, such as at the IARC level.

Future trends in epidemiology could lead to fingerprinting exposure through biomarker techniques borrowed from molecular biology. They might offer more direct indicators of risk. Sensitivity at low doses, however, is still a constraint.

Genotyping at work is not permitted in many countries due to its uncertainties and ethical implications. But the study of some repair genes of workers in nuclear power plants has already yielded information on individual sensitivity for workers at risk of oxidative damage, like smokers exposed to radiation (Aka, 2005).

Conclusions

Advancing knowledge about the health effects of low-dose ionizing radiation supports the use of a linear non threshold hypothesis for the dose-effect relationship and can be regarded as a precautionary approach for the dose range of occupational exposures.

Particular attention should be paid to genetic susceptibility and the ethical issues of genotyping. Higher exposures among medical imaging staff (interventional radiology and PET, possibly combined with CT) and medical exposure of children are also particular concerns.

Exposure of outside workers in the nuclear and non-nuclear industries and in medical settings requires appropriate management and follow-up. Systematic optimisation of protection can be of major assistance here, as has been demonstrated in nuclear power plants.

It illustrates how the linear non threshold hypothesis can be combined with operational flexibility and health protection. ■

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