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Health effects due to radiation from the Chernobyl accident

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Scope

The accident at Chernobyl occurred 25 years ago, on April 26th 1986.
The UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) has only very recently published its 2008 Report (UNSCEAR 2011) concerning the "Health effects due to radiation from the Chernobyl accident". This report has been discussed and approved in mid-2008 and the coverage of literature practically finishes at this time.
At the occasion of the 25th anniversary of the Chernobyl accident, the present article tries to give an up to date state of the art regarding the radiation-induced health effects from this accident, taking particularly into account recent scientific findings and publications. Unfortunately it was not possible for the author to take due account of the large number of non translated publications by Ukrainian, Russian and Byelorussian researchers. By the way, it is surprising that the competent international organizations did not give more interest in translating these multiple publications, particularly those on children's morbidity. This will be a real challenge in the future if we really want to cover correctly the situation.
Note that early health effects as acute radiation syndrome are not in the scope of this article.

Radiation doses to the most exposed population groups

The greatest sources of radiation dose from Chernobyl were, at different time periods, intake of short-lived radioactive iodines (particularly ^{131}I), external exposure from radionuclides deposited on the ground (particularly ^{95}Zr + ^{95}Nb, ^{103}Ru, ^{106}Ru, ^{132}Te + ^{132}I, ^{140}Ba + ^{140}La, ^{141}Ce, ^{144}Ce, ^{134}Cs and ^{137}Cs) and ingestion of radioactive caesium's (particularly ^{134}Cs and ^{137}Cs). In the near field (about 20 km) of the damaged reactor, fuel particles (with long-lived radionuclides such as $^{238\text{-}242}Pu$ and $^{21\text{-}243}Am$) made up the most important part of the deposited material, together with more than 90% of the $^{89\text{-}90}Sr$. Part of the $^{89\text{-}90}Sr$ was in water-soluble and exchangeable form and asked for remedial action to avoid contamination of the Dniepr system (principal source of freshwater supply in Ukraine) (Berkovski 1996, UNSCEAR 2011).
Three major groups of people were exposed to and, to a variable extent, are still being exposed to radioactive contamination:
1. Workers (liquidators, or emergency and recovery operations workers). Those individuals who were involved in emergency response, containment, clean-up and associated activities at the Chernobyl site and in the contaminated areas are commonly referred to as liquidators. This group consists of approximately 600 000 individuals, of whom about 240 000 worked in 1986 and 1987, when doses were highest, at the reactor site and the surrounding 30 km zone.

2. Inhabitants who were evacuated or relocated from contaminated areas. In the months following the accident about 116 000 people were evacuated from areas surrounding the reactor in Belarus, the Russian Federation and Ukraine. A further 220 000 people were relocated after 1986.
3. Inhabitants of contaminated areas who were not evacuated. About 5 million people continue to live in areas of Belarus, Ukraine and Russia that were contaminated by the accident (by convention, contaminated areas were defined as areas where the average deposition density of ^{137}Cs exceeded 37 kBq/m$^{2)}$.
The average effective dose received by the recovery operation workers between 1986 and 1990, mainly due to external irradiation, is now estimated at about 120 mSv. The recorded worker doses varied from less than 10 mGy to more than 1,000 mGy, although about 85% of the recorded doses were in the range 20–500 mGy. Uncertainties in individual dose estimates vary from less than 50% to up to a factor of 5 (UNSCEAR 2011). There is not enough information to estimate reliably the average thyroid dose for the recovery operation workers (UNSCEAR 2011, Chumak 2007, Bouville 2006).
The effective dose estimates for individuals in the general population accumulated over the 20 years following the accident (1986–2005) range from a few mSv to some hundred mSv depending on location, age and lifestyle factors, such as diet, or time spent outdoors. These doses are mainly due to external exposure from a mixture of deposited radionuclides, as well as to internal exposure from intake of ^{134}Cs and ^{137}Cs (UNSCEAR 2000 quoted by Cardis 2006; Bouville 2007).
The mean effective dose accumulated up to 2005 among residents in the strict control zones (with ^{137}Cs deposition density of 555 kBq/m^2 or more) is of the order of 50 mSv, while in less contaminated areas it is of the order of 10 mSv (Cardis 2006, UNSCEAR 2011).
The highest organ-specific dose was to the thyroid gland, primarily from ingestion of milk contaminated with radioactive iodines, particularly ^{131}I. A wide range of thyroid doses was received by the inhabitants of the contaminated areas in the three affected countries. Doses varied with age at the time of the accident, level of ground contamination and rate and source of milk consumption.
A study was published recently regarding reconstruction of thyroid doses following the Chernobyl accident. A population-based case-control study of thyroid cancer has been carried out in contaminated regions of Belarus and Russia among persons who were exposed during childhood and adolescence to fallout from the Chernobyl accident. For each study subject, individual thyroid doses were reconstructed for the following pathways of exposure: (1) intake of ^{131}I via inhalation and ingestion; (2) intake of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and radiotelluriums (^{131m}Te, ^{132}Te) via inhalation and ingestion; (3) external dose from radionuclides deposited on the ground; and (4) ingestion of ^{134}Cs and ^{137}Cs. A series of intercomparison exercises validated the models used for reconstruction of average doses to populations of specific age groups as well as of individual doses. Median thyroid doses from all factors for study subjects were estimated to be 0.37 and 0.034 Gy in Belarus and Russia, respectively. The highest individual thyroid doses among the subjects were 10.2 Gy in Belarus and 5.3 Gy in Russia. Iodine-131 intake was the main pathway for thyroid exposure. Estimated doses from short-lived radioiodines and radiotelluriums ranged up to 0.53 Gy. Reconstructed individual thyroid doses from external exposure ranged up to 0.1 Gy, while those from internal exposure due to ingested caesium did not exceed 0.05 Gy. The uncertainty of the reconstructed individual thyroid doses, characterized by the geometric standard deviation, varies from 1.7 to 4.0 with a median of 2.2. (Drozdovitch 2010).

Maybe the major think to underline regarding radiation doses to the exposed population is their huge *variability*, largely due to the consumption of *wild foods*, especially mushrooms, and *locally produced foods*, by a large part of the local population. This has a major influence on any attempt to interpret or predict the effects of the accident on the health of (subsets of) the population.

Radiation induced thyroid cancers

An increase in the incidence of thyroid carcinoma in children was noted in the hospitals caring for the population of the most exposed areas as early as 5 years after the accident in Belarus and slightly later in the Ukraine and the Russian Federation (Cardis 2005). To date, thyroid cancer has been the main direct consequence of exposure to fallout in the population in Belarus, northern Ukraine, and the oblasts of the Russian Federation closest to Chernobyl.

The issue of radiation induced thyroid cancers, the most striking effect of this accident, had been thoroughly discussed on 26 November 1998 during the EC (European Commission) scientific seminar "Thyroid diseases and exposure to ionising radiation: Lessons learned following the Chernobyl accident" (EC 2000) and, very recently (November 2010), updated by Sir Dillwyn Williams, during the EC scientific seminar on "Issues with internal emitters" (Williams 2010). The present review of radiation induced thyroid cancers will be largely based on this last high level updating.

Causal relation

The susceptibility of the thyroid to radiation-induced cancer had been recognized, already before the accident in Chernobyl, in many studies, particularly for external irradiation and for exposure in childhood (Japanese atomic bomb survivors, infants exposed to therapeutic x-rays for several benign diseases,...). Nevertheless, epidemiological studies based on internal exposures, mainly patients exposed to ^{131}I for medical reasons, provided essentially negative information with regard to thyroid cancer induction, which at this time suggested that the risk was (much) lower than after external irradiation. But most of the available data were based on exposures of adults (EC 2000).
The current views confirm the conclusions drawn during the 1995-1996 international conferences about the consequences of Chernobyl and during the 1998 EC scientific seminar (EC 2000):

- the large rise in the incidence of confirmed cases of thyroid carcinoma in children exposed to fallout from the Chernobyl nuclear accident,
- the correlation of incidence and extent of fallout,
- the rapid drop in incidence to near normal figures in children born more than a few months after the accident,

all of which combine to show a causal relation between exposure and carcinogenesis induction.

Size of the thyroid cancer increase

The last UNSCEAR report mentions that a number of 6848 cases of thyroid cancer were reported between 1991 and 2005 in the three affected republics (the whole of Belarus and Ukraine and the four most affected regions of the Russian Federation) amongst those under age 18 years in 1986. There is no doubt that a substantial fraction of this excess incidence of thyroid cancer can be attributed to exposure to radioiodine due to the Chernobyl accident. (UNSCEAR 2011).
There are several uncertainties in establishing the *exact* size of the increase, either as an absolute number or as an increase in incidence. There is first a need to define the area studied. Comparing the incidence in exposed and unexposed areas may also be complicated by ethnic and environmental factors, and by the difficulty in defining unexposed areas, when most of Europe was exposed to low level fallout deposition. Perhaps the biggest problem is the increased ascertainment in areas designated as contaminated, where the general public and health professionals will be aware of the increased risks, and are more likely to undergo careful examination or participate in screening programmes. Observed increases in incidence must also be considered in the light of world-wide increases in the incidence of papillary carcinoma of the thyroid, in part at least due to increasing use of techniques like ultrasound and fine needle aspiration (Williams 2010).

Providing an accurate estimate of the number of thyroid carcinomas attributable to the Chernobyl accident to date is difficult because of the uncertainties involved, and the variables which will be discussed in relation to estimates of the risk per Gray. These also influence predictions of the future, the numbers expected up to 2065 in Europe have been estimated with large variations, for example as 15,700 (95% UI: 3,400-72,000) (Cardis 2006) or 92,627 (Malko, quoted in Yablokov, 2009). Anyway, although the long-term magnitude of risk cannot yet be quantified, it is expected, from many decades of follow-up of studies of populations exposed to external radiation, that Chernobyl-related thyroid cancers will continue to occur for many more years (Adams 2010). Moreover, if our current risk models are right about the absence of attenuation of the ERR with attained age (or time since exposure) then we have seen up to now only the

tip of the iceberg and many thousands of cases of thyroid cancer are still to come among those heavily exposed to radioiodine in childhood (Wakeford 2011).

Radiation signature?

A recent study shows that seven genes allow to completely distinguish post-Chernobyl thyroid papillary carcinomas from sporadic thyroid papillary carcinomas (Port 2007). However, a previous study concluded on the absence of a specific signature in post-Chernobyl thyroid cancers. The authors investigated gene expression in sporadic papillary carcinomas and in post-Chernobyl thyroid cancers by a variety of microarray methods: the results suggest that these gene expressions cannot be distinguished, although both tumours are clearly distinct from autonomous thyroid adenomas. Post-Chernobyl, radiation-induced thyroid cancers and sporadic thyroid papillary carcinomas thus most likely represent the same disease. The authors did not exclude the possibility that further analysis will demonstrate that the post-Chernobyl carcinomas might belong to a more homogeneous restricted subset of carcinomas (Detours 2005). The issue is still in discussion.

Thyroid Carcinoma risk and the modifying factors

A number of epidemiological studies of thyroid cancer following exposure to radioactive iodines from the Chernobyl accident have been reported both in the most contaminated countries and in other European countries. Estimates of the risk/Gy vary greatly, with excess relative risks (ERR) from 2.15 (Zablotska 2010) to more than 50/Gy (Kopecki 2006). The results in general had wide confidence limits. The studies differ in a number of ways, the area studied, the level of exposure, the time over which the cases were collected, the level of confirmation of the diagnosis and the type of study (ecological or case control) (Williams 2010).
The ERR derived in the case–control and cohort studies –i.e. analytical studies in which information is collected at the individual level - are all similar, though slightly lower than the estimate from studies of external radiation (around 7/Gy), while ecological studies show generally larger ERR (Cardis 2006, Ron 1995, Ron 2007).

Reporting an overall figure for the risk of developing thyroid carcinoma after exposure to radiation conceals the effects of a number of variables. The major one is age at exposure. There is no doubt that young children exposed to external radiation are at a greater risk of developing thyroid cancer than older children, and that adults exposed to external radiation have much lower risk. There is also no doubt that in the population exposed to fallout after Chernobyl the risk of developing thyroid cancer was greatest in young children, falling rapidly with increasing age at exposure. The substantial increase in thyroid cancer incidence seen amongst those exposed as children or adolescents in Belarus, the Russian Federation and Ukraine since the Chernobyl accident shows no signs of diminishing up to 25 years after exposure (Williams 2010, Cardis 2006, Fuzik 2010).
As mentioned by Williams (Williams 2010),

- a pooled analysis of 7 studies of radiation induced thyroid cancer found the risk/Gy 5 fold higher in those under 4 at exposure when compared to those aged 10-14 (Ron 1995);
- a study of thyroid carcinomas as second tumours in children receiving radiotherapy for the first tumour found a ten fold difference in ERR/Gy between those treated under 1 year of age, and those aged 15-20 (Ronckers 2006);
- the Chernobyl data suggest a similar ratio, although possibly with the first 3 years of life being particularly sensitive.

Information on thyroid cancer following *in utero* iodine-131 or external radiation exposure is very limited, including in populations exposed to fallout from the Chernobyl nuclear accident. A recent study suggests that in utero exposure to radioiodines may have increased the risk of thyroid carcinoma approximately 20 years after the Chernobyl accident, but the epidemiological evidence to date is not sufficient to accurately quantify a difference in risk between prenatal and early postnatal exposure (Hatch 2009).

Most studies agree that the risk to those exposed as adults, if present, is likely to be small. This issue has been again evaluated in 2009 among A-bomb survivors who were adults (20 years of older) at the time of the bombings (Richardson 2009). Estimated thyroid doses were positively associated with thyroid cancer incidence, but only among women (ERR/Gy 0.70; 90 % CI: 0.20-1.46). A recent study (Fuzik 2010) suggests that there may be an increased incidence in those exposed as adults at all ages, and also that there may be a longer latent period in those exposed at older ages. These are both important points, but this study seems to have a major problem with ascertainment (Williams 2010).

Another major variable affecting risk is the level of dietary iodide. Administration of stable iodide shortly before or within a few hours after exposure can of course block the uptake of radioactive iodine, but few of those exposed after Chernobyl received stable iodine within those time constraints.
The role of iodine deficiency and of dietary intake was studied by Cardis et al in 2005. The risk for thyroid cancer in areas with severe iodine deficiency was found to be approximately three fold that in areas with normal iodide levels. This study also showed that long term supplementary iodide intake after the accident lowered the risk in both the higher and lower iodide levels (Cardis 2005).
The use of long-term dietary iodide administration in populations exposed to fallout containing radioactive iodine should then be considered, particularly in iodine deficient areas.

These two variables (age at exposure and level of dietary intake) combine when considering how to express the risk of developing thyroid carcinoma after exposure to fallout. The ERR/Gy will be affected by both, and it will be necessary to specify the group referred to, for example children under 3 from an iodine deficient area, rather than imply that a single ERR is generally applicable. (Williams 2010)

Other factors relevant to the risk of developing thyroid carcinoma after radiation exposure include genetic susceptibility. Polymorphic variants of DNA repair genes such as XRCC and ATM have been associated with an increased risk of radiation induced thyroid cancer, both after Chernobyl and after exposure to nuclear tests, but they have also been linked to sporadic thyroid cancers (Williams 2010, Adjadj 2009, Akulevitch 2009, Bastos 2009).

Clinical aspects

Studies of the consequences of the Chernobyl accident allow studies of the changes with latency, as there have been such a large number of cases of one type of tumour where it can be presumed that the mutation initiating the carcinogenic process occurred within a few days or weeks of April 26th 1986. With increasing latency the papillary carcinomas (PTCs) that form the great majority of the radiation induced cases have become smaller in size, and clinically less aggressive (Williams 2010, Demidchik 2006). Pathology studies have shown that the PTCs are more mature, with solid type tumours predominating in the early cases, and classic type PTCs in the later cases. Molecular findings in the PTCs have also changed with latency, initial studies found that almost all showed a RET-PTC rearrangement, dominantly RET-PTC3. With increasing latency the proportion of cases with RET-PTC rearrangements has fallen, and an increasing proportion of these have been RET-PTC1 (Williams 2010). Molecular studies are still ongoing.

To date, thyroid cancer has been the main direct consequence of exposure to fallout in the population in Belarus, northern Ukraine, and the oblasts of the Russian Federation closest to Chernobyl. There is currently no doubt that in this population the risk of developing thyroid cancer was by far the greatest in young children, falling rapidly with increasing age at exposure. If our current risk models are right about the absence of attenuation of the excess relative risk with attained age (or time since exposure) then we have seen up to now only the tip of the iceberg and many thousands of cases of thyroid cancer are still to come among those heavily exposed to radioiodine in childhood.

Radiation induced thyroid diseases other than thyroid cancers

Some recent studies and reviews have evaluated the incidence of radiation induced thyroid diseases other than thyroid cancers (Hatch 2010, Ron 2010, Agate 2008, Ostroumova 2009).
In a recent review, Ron and Brenner (Ron 2010) tried to evaluate the evidence regarding structural (tumours, nodules), functional (hyper- and hypothyroidism), and autoimmune thyroid diseases. After a wide range of doses of ionizing radiation, an increased risk of thyroid adenomas and nodules was observed in a variety of populations and settings, with a dose response appearing linear at low and moderate doses. They also concluded that considerably less consistent findings are available regarding functional and autoimmune thyroid diseases. Although the data are limited, acute radiation induced thyroiditis is known to occur after 131 I treatment of Grave's disease or external-beam radiotherapy and is considered to be a high-dose phenomenon. On the contrary chronic thyroiditis (chronic autoimmune thyroiditis or Hashimoto thyroiditis) is regarded as a possible long-term consequence of thyroid gland irradiation at low to moderate doses, but the studies regarding this issue (A- bomb study, Nevada nuclear test site, Marshall Islands and Chernobyl) have provided until now conflicting results.
As regards the Chernobyl data, the authors of a recent study (Agate 2008) on children living in contaminated Belarussian settlements (13- 15 years after the Chernobyl accident), reported that the autoimmune reactions initially observed in several studies (6 to 8 years after the accident) are still present but with lower levels of thyroid autoantibodies, while thyroid function remains normal. These data suggest that the elicited autoimmune reaction may have been transient, without triggering long term clinical autoimmune thyroid disease. Longer observation periods are nevertheless needed to exclude later effects (Agate 2008), as an increasing risk of autoimmune thyroiditis with increasing thyroid dose has been reported after a long follow up, as in the most recent analysis of the Nevada cohort (age at exposure less than 7 year, time since exposure 24-35 years) (Lyon, 2006).

Radiation induction of cancers other than thyroid cancers

Leukaemia's

Amongst adults, the most meaningful evidence comes from studies of recovery operations workers.
Recent case-control studies on Chernobyl liquidators from Ukraine (Romanenko 2008) and from Belarus, Russia and the Baltic countries (Kesminiene 2008) found significantly increased ERR, with a linear dose-response in the Ukraine study. These studies used individual bone marrow radiation doses estimated by the recently developed RADRUE dose reconstruction method. Although the pattern of results from these two studies is rather unusual and further investigation is required to properly understand the finding, these nested case-control studies do suggest a radiation-related risk of leukaemia among the liquidators (Wakeford 2011).
Following the Chernobyl nuclear reactor accident in 1986 a study found a notably raised risk (ERR per Gy 78.8; CI 22.1-213) of childhood leukaemia in the heavily contaminated districts of the Ukraine (but not in Belarus or Russia) (Davis et al 2006). As the results could be due to a sampling-derived bias in Ukraine, the authors concluded that this study provides no convincing evidence.
In a later study in the Ukraine (Noshchenko 2010), the risk of leukaemia was still significantly increased among those with radiation exposure doses higher than 10 mGy, but the risk estimate was substantially lower, raising questions about the accuracy of the data used in these studies (Wakeford 2010).

Breast cancer and other solid cancers

Apart from thyroid cancers and leukaemia's, there are currently few other clear evidence of increase in the incidence of cancers in the most affected populations, with the possible exception of breast cancer. A study was conducted in Belarus and Ukraine to describe the spatial and temporal trends in breast cancer incidence. This study demonstrated increases in breast cancer incidence in all areas, reflecting improvements in cancer diagnosis and registration. But a significant 2-fold increase was observed, during the period 1997-2001, in the most contaminated districts (average estimated cumulative dose of 40 mSv or more) compared with the least contaminated districts. The increase was highest among women who

were younger at the time of the exposure. The authors concluded that it is unlikely that this excess could be entirely due to the increased diagnostic activity in these areas (Pukkala et al 2006).

Many of the cancer consequences of exposure to atomic bomb radiation were not observed until decades after the event, so that other non-thyroid cancers will probably occur in the future in those exposed to fallout, particularly as there are major uncertainties over the individual doses from the Chernobyl accident. It is certainly wrong to consider that we are "at the end of the story" (sic) and it will be necessary to continue for a long time the follow up of these populations.

Hereditary effects

Several studies were conducted concerning increases in the rate of minisatellite[1] DNA mutations in children born to exposed parents after Chernobyl. Studies in exposed families from rural areas of Ukraine and Belarus are indicative of a statistically significant elevated paternal mutation rate in the exposed families (1.6 –fold increase) (Dubrova 1996, 2002).
A similar effect has been seen in the children and grand-children of men exposed to weapons testing in Semipalatinsk (Dubrova 2002) and among irradiated families from the Techa River population (Dubrova 2006).
However, studies conducted in families of Chernobyl cleanup workers globally failed to show increases in the minisatellite mutation rates (Livshits 2001; Kiuru 2003: slight increase above 200 mSv; Slebos 2004: modest increase, not statistically significant; Furitsu 2005). The only clearly positive study (Weinberg 2001) has been criticised for the methodology used (Jeffreys and Dubrova 2001).
Finally no effect on minisatellite DNA mutations has been found in studies on the survivors of the atomic bombing and on radiotherapy patients (exposures due to *external* radiation).
As the human experimental data have been so far derived from studies with small numbers of families, as the increases of mutation rates were seen in populations from areas contaminated with internal emitters but not in those exposed to external radiation sources and as current data fail to establish reliable dose-effect relationships, further studies are essential to address this issue (Bouffler 2006).

A parallel phenomenon, tandem repeat (ESTR) instability, is described in mice, where this instability is shown to be *transgenerational* (transmission of genomic instability via the germline to future generations). Consequences of transgenerational genomic instability includes cancer predisposition among the offspring of irradiated parents and other genetic endpoints, but available evidence is currently limited to animal studies (Barber 2006, Bouffler 2006). Noteworthy several studies on organisms exposed to contaminated zones at Chernobyl are showing an increased risk of mutation in the germline (for example barn swallows) (Bouffler 2006). Yet the quality of the barn swallows study has been disputed and these results need therefore careful interpretation (Smith 2008).
The human clinical significance of mini-satellite mutations is still very uncertain, but "associations" are described with various diseases and pathogenic mechanisms and we have currently also no knowledge as to whether minisatellite mutations play any role in determining pregnancy outcomes (Bouffler 2006, Gatchel 2005). Further research is then needed, including in the offspring of persons exposed after Chernobyl, as underlined in the ARCH strategic long term research agenda for the health consequences of the Chernobyl accident (ARCH 2011).

[1] Current genetic risk estimates for radiation are mainly based on measurement of mutation frequencies in the mouse using some marker genes. In recent years analysis of mouse and human DNA sequence has shown that some regions containing repetitive sequence elements, collectively known as tandemly repeated DNA loci (TRDLs), mutate at a much higher frequency (x 1000) than the marker genes, allowing detecting changes in mutation rate in relatively small population samples. Additionally, these mutations seem to occur far to the sites of DNA damage (untargeted effect) and also long after the radiation exposure (delayed effect) and appear to be predominantly *point* mutations. TRDLs are represented by relatively short microsatellites, long expanded simple tandem repeats (ESTRs in mouse) and longer minisatellites (used as markers for germline mutations in humans). Notably minisatellite mutations most probably occurs during meiosis in germ cells (this means during all life in men but only in the early stages of in utero life in women, where oocytes are already formed during embryogenesis) (Bouffler 2006).

New molecular techniques, that overcome some of the classical limitations, are currently being developed to test germ line mutagenicity in humans (Verhofstad 2008).

Birth defects

Although there have been many claims of an increased incidence of congenital anomalies in children born shortly after the accident (Yablokov 2010, Busby 2009), possible birth effects due to Chernobyl accident are not dealt with in recent UNSCEAR publications (UNSCEAR 2011), the reason being that the majority of the committee considered evidence was totally lacking. This may be partly due to the difficulty to separate Chernobyl-related abnormalities from those due to other causes or from the effects of increased ascertainment. A major observation in this respect was that the prevalence at birth of the malformations recorded in the congenital anomalies registry in Belarus showed a similar positive trend in areas of low and high contamination and was even *lower* in the most contaminated regions (Lazjuk 2003). Although the authors mentioned that the prevalence rates were assessed at the oblast level, a level of aggregation that hides the heterogeneity of the distribution of contamination inside each region, this being susceptible to be an ecological bias, this study has been considered by many as offering compelling evidence of the absence of Chernobyl-related birth defects.
Yet new data have been provided later calling for more balanced conclusions.
In the framework of the Eurocat[2] Workshop on Environmental Pollution organized in Budapest on 6-7 March 2007, results of current research on environmental pollution and congenital anomalies in Belarus have been presented. The time trend analysis of the prevalence at birth of congenital anomalies has been extended from the large (oblast) administrative division of Belarus to smaller entities (*district*), allowing taking more precisely into account the real degree of contamination. A clear excess of the congenital anomalies under study was then observed in the highly contaminated districts *during the three first years* after the accident, when registered prevalence rates significantly exceeded as well the pre-accidental values as the rates in low-contaminated areas. The main contributors to this increase were polydactyly, reduction defects of limbs and the group of multiple congenital malformations. The (relatively common) skeletal anomalies are considered to be of multifactorial nature but with a considerable (dominant) mutational component. (Zatsepin 2007, FANC-SCK 2005).
An analysis of monthly prevalence revealed also a Down syndrome cluster (2-3 times higher than expected) in January of 1987 (9 months after irradiation). The time of appearance and the spatial distribution of cluster cases suggest an association with the exposure during the first days/weeks after accident due to substantial release of short-lived radionuclides when exposure dose rates exceeded natural background levels by 1-3 orders of magnitude on considerable part of Republic of Belarus. Contribution of the main risk factor (maternal age) has been excluded. Meiotic disjunction failure resulting in aneuploidy in the offspring of exposed animals is a well known effect of ionizing radiation, the hours around fertilization being especially susceptible. Thus, conception of aneuploid human embryos during the period of relatively high exposure dose rates could be a possible consequence of irradiation of the vulnerable meiotic stages (Zatsepin 2004).

A recent study conducted by a researcher of the University of South Alabama (Wertelecki 2010) was focused on the Ukraine oblast of Rivne, and in particular on the Rivne sub-region of Polissia, where one of the populations most exposed to chronic low-dose radiation from Chernobyl lives in. This study shows that, among 96 438 births in Rivne between 2000 and 2006, the overall rate of neural tube defects (including spina bifida) is among the highest in Europe (22.2 vs 9 per 10 000 live births). The rates of conjoined twins and teratomas also seem to be elevated. In Polissia, the overall rates of neural tube

[2] Eurocat (European Surveillance of Congenital Anomalies) is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies. The network started in 1979, covers 29% of European birth population through 43 registries in 20 countries.

defects are even higher (27.0 vs 18.3, respectively; odds ratio: 1.46 [95% confidence interval: 1.13–1.93]), and the rates of microcephaly and microphthalmia may also be elevated.
The malformation patterns observed suggest early disruptions of blastogenesis, manifesting as alterations of body axes, twinning, duplications, laterality, and midline formation. The limitations of this study include a lack of data regarding levels of low-dose radiation, diet, consumption of micronutrients (possible folate deficiency in particular), degrees of consanguinity and prenatal alcohol exposure. As the author underlines, these factors could also combine their effects.
A subsequent study (Dancause 2010) tried to determine current radiation exposure routes in Rivne-Polissia, through a dietary and activity survey to 344 women in Polissia. Alcohol intake was low and alone does not account for the observed high rates of birth defects. Wild foods, especially mushrooms and berries, and locally produced foods, especially milk related, were major radiation exposure routes. The authors concluded that, twenty four years after the Chernobyl accident, women continue to be chronically exposed to low-dose radiation at levels exceeding current recommendations and this might contribute (especially synergistically with alcohol consumption and micronutrient deficiencies) to higher prevalence of birth defects in areas with high levels of radiation contamination compared to uncontaminated areas.

Although these results are limited and possible confounding factors typical for descriptive epidemiological studies prevent from drawing final conclusions, this sensitive issue needs further consideration for example through high quality analytical studies in exposed populations.

Other Non Cancer Diseases

Children's morbidity

There are many claims concerning the health of children in the contaminated territories around Chernobyl, which seem to suffer from multiple diseases and co-morbidities with repeated manifestations (compilation in Yablokov 2009). Unfortunately the reports from international organizations did not give until now much interest in the multiple publications by Ukrainian, Russian and Byelorussian researchers on children's morbidity. This is partly due to the fact that many of these studies were not available in English but also to the fact that they often did not meet the scientific and editorial criteria generally required in the Western peer reviewed literature. The tone of Yablokov's book also produced an uneasy feeling in readers (Jackson 2011). Anyway, it is really surprising that the competent international organizations did not judge necessary to translate these multiple publications.

More or less recent studies brought again this issue into light, including the debated publications of Bandazhevsky (Bandazhevsky 2001), linking ^{137}Caesium body loads with ECG alterations and cardiovascular symptoms in children such as arterial hypertension, and the studies on neurobehavioral and cognitive performances in children of the contaminated areas (for example Loganovsky 2008).
To verify these observations, IRSN conducted series of animal studies. Rats were exposed to ^{137}Caesium contamination during several months (generally 3 months, sometimes 9) through drinking water containing 6500 Bq/L. Intake of ^{137}Caesium was estimated to be 150 Bq/day/animal (500 Bq/kg of body weight), a figure that is considered by the authors to be comparable with a typical intake in the contaminated territories (based on Handl's evaluation in Ukraine: 100 Bq/day with variations, according to geographical location and diet, from 20 up to 2000 Bq/day as in the case of special dietary habits like excess consumption of mushrooms) (Handl 2003).
Although the animals tested in theses studies did not show induced clinical diseases, a number of important biological effects were observed on various systems: impairments in the cardiovascular system such as an increase of CK and CK-MG, markers of possible heart muscle damage; decrease of mean blood pressure and disappearance of its circadian rhythm (Guéguen 2008); in the Central Nervous System: EEG modifications, perturbations of the sleep-wake cycle, regional ^{137}Caesium accumulation in the brain stem (Lestaevel 2006); molecular modifications of pro- and anti-inflammatory cytokines and NO-ergic pathway in the brain, indicators of a neuro-inflammatory response, particularly in the hippocampus (Lestaevel 2008); and in various metabolic systems : alteration of vitamine D metabolism, associated with a dysregulation of mineral homeostasis (Tissandie 2008); alteration of testicular and

adrenal steroidogenesis (Grignard 2007). These somewhat scattered results are difficult to interpret and the link between all these modifications is far from being obvious.
It must be underlined that these somewhat unexpected results are obtained after relatively modest intakes of ^{137}Caesium and that a fraction of the population in the contaminated territories has been shown to incorporate ten times more ^{137}Caesium with their food. This justifies further investigation in this field. IRSN is currently performing a clinical research (EPICE) on children in the area of Bryansk, particularly on cardiac rhythm and ECG perturbations. First results would be available in 2013.
On the ground of the fact that there is a currently a lack of analytical studies in which dose and risks on non-cancer diseases in children were estimated on an individual level, a series of longitudinal studies have also been initiated recently in Ukraine in conjunction with the US University of South Carolina and were devoted to children's health, making use of the fact that all children in the studied territory had been obliged to participate in a yearly medical examination.
A first study (Stepanova 2008) investigated, for the years 1993 to 1998, the association between residential soil density of ^{137}Caesium (used as exposure indicator) and blood cell concentrations in 1251 children. The data showed a statically significant reduction in red and white blood cell counts, platelet counts and haemoglobin with increasing residential soil contamination. Over the six-year observation period, hematologic markers did improve. The authors draw the attention on the fact that similar effects and evolution were reported after the Techa River accident in 1957. (Akleyev 1995)
A second study (Svendsen 2010) investigated, for the same years 1993 to 1998, the association between residential soil density of ^{137}Caesium and spirometry measures in 415 children. They found statistically significant evidence of both airway obstruction and restriction with increasing soil ^{137}Caesium. The authors advance as possible explanation a radiation-induced modulation of the immune system leading to recurrent infections and finally to detrimental functional effects.
Series of other studies are announced. The authors of these studies conclude by saying that the current "optimism of the UN reports may be based on too few studies published in English, conducted too soon after the event to be conclusive".

Although there are many claims concerning the health of children in the contaminated territories around Chernobyl, the reports from international organizations did not give until now much interest in the multiple publications by Ukrainian, Russian and Byelorussian researchers on children's morbidity. The translation and evaluation of these multiple publications will be a real challenge in the future if we really want to cover correctly the situation. We also really need further good quality research on morbidity in children living in contaminated territories. This is our ethical duty towards this population and, moreover, it may have major influence on our evaluation of the radiotoxicity, particularly for children and infants, of major radioisotopes susceptible to cause chronic internal exposures of the population in any future nuclear accident.

Morbidity of liquidators, particularly heart diseases

As for children living in contaminated territories, numerous studies have been published concerning non cancer diseases in liquidators, many of them also not published in English, and often being controversial due to a number of biases and confounding factors. As mentioned in the ARCH strategic research agenda, due to the lack of complete high-quality disease registries for non-cancer outcomes, specific studies of appropriate groups of liquidators are needed, in particular regarding cardiovascular and cerebrovascular diseases.
In a study on a Russian cohort of 61,000 Chernobyl emergency workers observed between 1986 and 2000, a statistically significant risk of ischemic heart disease was observed [ERR per Gy = 0.41, 95% CI 0.05 to 0.78]. The mean dose was 109 mGy (Ivanov 2006). There was also a significant risk for cerebrovascular diseases [ERR per Gy = 0.45, 95% CI 0.11 to 0.80].
In a sub-cohort of 29,000 emergency workers who arrived in the Chernobyl zone during the first year after the accident and whose the mean dose was greater than 150 mGy, the ERR per Gy was smaller and non significantly increased for ischemic heart disease, while it was still significantly increased for cerebrovascular diseases (0.39, CI 0.004 to 0.77).
However, the radiation risks in this large-scale cohort study were not adjusted for recognized risk factors such as excessive weight, hypercholesterolemia, smoking, alcohol consumption, and others.

New data on these issues and the underlying mechanisms would be available at the end of 2011 coming from the EU FP7 CARDIORISK project.

Cataracts

During the EU Scientific Seminar held in Luxembourg on 17 October 2006 about "New Insights in Radiation Risk and Basic Safety Standards", Norman J. Kleiman, Director of the Eye Radiation and Environmental Research Laboratory in the Columbia University reviewed the new available evidence regarding radiation-induced cataracts (EC 2007). The most recent findings from the Ukrainian American Chernobyl Ocular Study (UACOS) (established in 1996 to monitor the effects of this radiation exposure on the eyes of clean-up workers), support a significant lowering of the supposed cataract "threshold" radiation dose (Worgul 2007). The evidence points to a dose threshold no greater than 700 mGy.
Concerning Chernobyl, a new study had been published. In 2007, Chumak et al. investigated the lens dosimetry in the above-mentioned study of a cohort of exposed clean-up workers (liquidators) at the Chernobyl Nuclear Power Plant and concluded that the current dosimetric methodology provides reasonable estimates of individual γ-ray and ß-particle doses to the lens of the eye that are sufficiently accurate to have utility in this kind of epidemiological/clinical study.
No new study regarding Chernobyl effects on cataracts have been published up to date.
Let us remind that an older study (Day 1995) showed a small but statistically significant excess of subclinical posterior subcapsular lens changes in 5-17 y old Ukrainian children residing around Chernobyl.
A recent review performed by a team including HPA experts (Ainsbury 2009), concluded that recent studies indicate that the threshold for cataract development is certainly less than was previously estimated, of the order of 0.5 Gy, or that radiation cataractogenesis may in fact be more accurately described by a linear, no-threshold model.

Follow up and research needs

Many of the cancer and non-cancer consequences of exposure to atomic bomb radiation were not observed until decades after the event, so that other thyroid and non-thyroid effects may occur in the future in those exposed to fallout, particularly as there are major uncertainties over the individual doses from the Chernobyl accident (Williams 2010, Baverstock 2006). It is therefore necessary to continue the follow up of these populations. This follow up should make use of well-designed analytical epidemiological studies with careful individual reconstruction and choice of appropriate controls (Cardis 2007).

In this spirit, and in the framework of the European Commission FP7, a project has been conducted to propose a strategic long term research agenda for the health consequences of the Chernobyl accident (project ARCH: Agenda for Research on Chernobyl Health). The creation of a Chernobyl Health Effects Research Foundation, similar to the well known RERF in Japan, has also been suggested. Let's hope that these initiatives will be supported.

In this context, it is important to realize that there are still *major uncertainties* regarding the assessments of risks induced by internal contaminations. The simple use of the concept of effective dose and its calculation through the dose conversion factors (Sv/Bq) may be misleading for risk assessment (IRSN 2005, CERRIE 2004), as illustrated by Müller's experiments on embryos in the preimplantation stage: due to the highly heterogeneous distribution (specific incorporation within DNA), ^{3}H-thymidine, for example, is between 1,000 and 5,000 times more effective (to produce deleterious effects) than HTO when the *same activity* is applied! These effects are still more pronounced using ^{3}H-arginine (histone precursor). We should be more cautious before claiming that some results are not acceptable, just because they cannot be explained by the conventionally calculated effective dose.
We really need further good quality research on morbidity in children living in contaminated territories. This may have major influence on our evaluation of the radiotoxicity, particularly for children and infants,

of major radioisotopes susceptible to cause chronic internal exposures of the population in any future nuclear accident

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For clarity, references have been grouped by themes: first the reviews, followed by radiation doses, thyroid cancers, other thyroid diseases, other cancers, hereditary effects, birth defects, children's morbidity, liquidators' morbidity and finally cataracts.

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