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Health Effects of the Chernobyl Accident and Special Health Care Programmes

Report of the UN Chernobyl Forum

Expert Group "Health"

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Foreword

Twenty years have passed since the worst nuclear reactor accident in the world occurred at the Chernobyl nuclear power plant in Ukraine. The radioactive contamination which resulted from the explosion and fire in the first few days spread over large areas of neighbouring Belarus and the Russian Federation, with most of the fallout in Belarus. While national and local authorities did not immediately disclose the scale of the accident, the mitigation measures, such as distribution of potassium iodine pills, food restriction, and mass evacuation from areas where the radioactive contamination was greatest, undoubtedly reduced the health impact of the radiation exposure and saved many lives.
The accident caused severe social and economic disruption and had significant environmental and health impact. This was aggravated by the political and economical changes in the three affected states related to the break-down of the Soviet Union. In the aftermath of the accident the international scientific and medical community collaborated closely with national experts dealing with health effects of the accident in the affected countries.

There is a substantial body of international collaborative projects on the situation, which should lead to advancement in radiation sciences. However, considerable speculation and disinformation remains about the possible health impact of the accident for the millions of affected people. To address the health, environmental and socioeconomic consequences of the Chernobyl accident, the United Nations in 2003 launched an Inter-Agency initiative, the Chernobyl Forum. The Forum's Secretariat, led by the International Atomic Energy Agency (IAEA), the World Health Organization (WHO), the United Nations Development Programme (UNDP), and several other international organizations collaborated with the governments of the affected countries. The purpose of the Chernobyl Forum was to review the consequences of the accident, issue technical reports and, based on this information, to provide authoritative statements and recommendations to the Governments of Belarus, the Russian Federation and Ukraine. An additional purpose of the Forum was to provide the information in non-scientific, appropriate languages (Russian and English) to the affected populations.

Under the Forum's auspices, the WHO's Radiation and Environmental Health Programme convened a series of international scientific expert meetings. They included scientists of international repute who had been conducting research on Chernobyl. This report is the outcome of WHO's contribution to the Forum.

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) review of the scientific literature on Chernobyl health effects published in 2000 was used in this review and updated with more recent information.

Many lessons have been learned from the Chernobyl accident and preparations have been made to respond to and mitigate future accidents. An international system of response to nuclear emergencies and radiological accidents has been established, including the WHO Radiation Emergency Medical Preparedness and Response Network.

Over the past 20 years, people in the three affected countries have come a long way in overcoming the consequences of the accident. Providing the public and key professionals with accurate information about the health and environmental consequences of the disaster should be a high priority. This report is the result of a sound scientific evaluation of the available evidence and provides a firm basis for moving forward.

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Cover illustration: includes original paintings by Natasha Karasyova, age 16 (*The Bird of the Earth*); Paulina Kuzmina, age 11 (*A Japanese*); and Roman Striga, age 16, (*Butterfly*). All artists are from the Children's Folk Art Studio, directed by R. Mye (Minsk, Belarus).

Contents

Chapter 1

GENERAL AND METHODOLOGICAL ISSUES

Introduction

The accident at the Chernobyl nuclear power plant in northern Ukraine on April 26, 1986 resulted in the release large amounts of radioactive materials, causing serious contamination of local regions and trace contamination throughout Eastern and Western Europe. These releases and subsequent transfers of radionuclides, mainly radioisotopes of caesium and iodine moving through air, water, and foods, caused radiation exposures of the workers involved in the clean up operations after the accident, those evacuated from nearby settlements, and those who continued to live in contaminated regions.

This report presents an updated review and evaluation of the health consequences of the accident that can be identified as caused by the radiation exposures from the accident in workers and the populations of the most affected regions of the former Soviet Union that are now the countries of Belarus, the Russian Federation, and Ukraine.

As background of the evaluation and a starting point for the present work, the latest review of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in the UNSCEAR 2000 report on health effects of the accident is first summarized. This was the most recent, comprehensive evaluation of the health consequences of the accident. Since many studies are on-going or newly initiated with new information continually becoming available, an independent, updated review of all published results is necessary.

The main evidence for the presence or absence of various health outcomes is provided by epidemiological investigations. It is necessary, however, to carefully review and understand the methodological issues and limitations of these studies in order to properly interpret the results. These background issues for the present evaluation are presented in Chapter 1.

The dosimetry assumptions or methods used in exposure evaluations are also key to clarifying the strength of relationships of effects to radiation exposures. The main features of dosimetry considerations are briefly summarized in Chapter 2.

In Chapter 3-6, the specific outcomes of epidemiological investigations are presented: thyroid disease, leukaemia, other solid cancers, non-cancer diseases and psychological effects. This report focuses primarily on the long-term health consequences of radiation exposures in Belarus, the Russian Federation and Ukraine. Cancer is currently thought to be the most consequential long-term stochastic effect of ionizing radiation (UNSCEAR, 2000), but other non-malignant disease outcomes are also considered.

In general, the approach taken in preparation of this report has been to first summarize the current evidence relating to each outcome, in particular, focusing on new studies that have appeared since the UNSCEAR 2000 report. This is followed by the assessment made by the various expert panels that were formed for compilation of this report. Within this assessment, each topic, e.g., epidemiology, biology, etc., is divided into a consensus, i.e., conclusions that the experts feel can reasonably be made at this time, followed by a section on gaps in knowledge that prevent full understanding or interpretation. Finally, a series of recommendations regarding future scientific research are provided within each discipline.

Because of the general interest in knowing the full scope of the accident, estimates of the number of deaths caused to date or projected over the lifetimes of those exposed are presented in Chapter 7. It must be noted that considerable uncertainty surrounds such estimates, as the radiation doses are mostly inadequately quantified, and available risk coefficients may not be applicable to the specific conditions of exposure following the Chernobyl accident, which involved protracted exposure periods at low dose rates to a population of different age, lifespan, and lifestyle features. With no means to adjust the risk coefficients or even to know their applicability to purposes other than radiation protection planning, the projected deaths can only be regarded as order of magnitude estimates. The estimates point to a total of several thousand deaths over the next 70 years, a number that will be indiscernible from the background of overall deaths in the large population group. The estimates do not substantiate earlier claims that tens or even hundreds of thousands of deaths will be caused by radiation exposures from the Chernobyl accident.

In Chapter 8, a description is provided of the various health care systems operating in Belarus, the Russian Federation and Ukraine. Included here are also recommendations that the expert group thought to be most appropriate in this area.

The objectives of this report are 1) to provide the scientific and lay community with an assessment of the current status of information regarding health consequences of the Chernobyl accident and 2) to provide appropriate authorities and agencies with a series of detailed recommendations for future directions both in research and with respect to the health systems operating in the three countries that have been most severely affected by the world's worst nuclear accident.

Background for the Evaluation

The Chernobyl accident caused the deaths of 30 power plant employees and firemen within a few days or weeks (including 28 deaths that were due to radiation exposure). In addition to those involved in early emergency operations, about 240,000 recovery operation workers (also called "liquidators" or "clean-up workers") were called upon in 1986 and 1987 to take part in major mitigation activities at the reactor and within the 30-km zone surrounding the reactor. Residual mitigation activities continued on a relatively large scale until 1990. In total, about 600,000 persons (civilian and military) have received special certificates confirming their status as liquidators, according to laws promulgated in Belarus, the Russian Federation, and Ukraine (UNSCEAR, 2000).

In addition, massive releases of radioactive materials into the atmosphere brought about the evacuation of about 116,000 people from areas surrounding the reactor during 1986, and the relocation, after 1986, of about 220,000 people from what are now three independent republics of the former Soviet Union: Belarus, the Russian Federation, and Ukraine. Vast territories of these three republics were contaminated to a substantial level. The population of those contaminated areas, from which no relocation was required, was about 5 million people.

The following paragraphs provide a summary of important observations and views of UNSCEAR, provided in their evaluation of the effects of the Chernobyl accident published in the UNSCEAR 2000 report. This was the latest general review of available information on the health effects of the accident.

A majority of the studies completed to date on the health effects of the Chernobyl accident have been of the geographical correlation type (also called ecological studies), which compares average population exposure with the average rate of health effects or cancer incidence in time periods before and after the accident. As long as individual dosimetry is not performed, no reliable quantitative estimates of impact on health can be made. The reconstruction of individual doses is a key element in future research on health effects related to the Chernobyl accident.

The number of thyroid cancers in individuals exposed in childhood, particularly in the severely contaminated areas of the three affected countries, is considerably greater than expected, based on previous knowledge. The high incidence and the short induction period have not been experienced in other exposed populations, and factors in addition to ionizing radiation are almost certainly influencing the risk. Some such factors include age at exposure, iodine intake and metabolic status, endemic goiter, screening for thyroid cancers in the affected populations, short-lived isotopes other than ^{131}I, higher doses than estimated, and, possibly, genetic predisposition. More than 4000 thyroid cancer cases have been reported in Belarus, the Russian Federation and Ukraine in children and adolescents for the period 1990-2002. Age seems to be an important modifier of risk. The influence of screening is difficult to estimate. Approximately 40% of the cases were found through screening programmes, and it is unclear how many of these cancers would otherwise have gone undetected. Taking the advanced stage of the tumors at time of diagnosis into consideration, it is likely that most of the tumors would have been detected sooner or later.

The present results from several studies indicate that the majority of the post-Chernobyl childhood thyroid carcinomas show the intra-chromosomal rearrangements characterized as *RET/PTC1* and *3*. There are, however, several questions left unanswered, e.g. the influence of age at exposure and time since exposure on the rate of chromosome rearrangements.

The risk of leukaemia has been shown in epidemiological studies to be clearly increased by radiation exposure. However, no increased risk of leukaemia linked to ionizing radiation has so far been confirmed in children, in recovery operation workers, or in the general population of the former Soviet Union or other areas with measurable amounts of contamination from the Chernobyl accident.

Increases in a number of non-specific detrimental health effects other than cancer in recovery operation workers and in residents of contaminated areas have been reported. It is difficult to interpret these findings without referring to a known baseline or background incidence. Because health data obtained from official statistical sources, such as mortality or cancer incidence statistics, are often passively recorded and are not always complete, it is not appropriate to compare them with data for the exposed populations, who undergo much more intensive and active health follow-up than the general population.

Some investigators have interpreted a temporary loss of ability to work among individuals living in contaminated areas as an increase in general morbidity. High levels of chronic diseases of the digestive, neurological, skeletal, muscular and circulatory systems have been reported. However, most investigators relate these observations to changes in the age structure, the worsening quality of life, and post-accident countermeasures such as relocation.

Many papers have been published in the last decade on the immunological effects of exposure to radiation from the Chernobyl accident. Since it is unclear, however, if possible confounding factors have been taken into account, such as infections and diet, it is difficult to interpret these results.

Methodological Issues of Epidemiological Investigations

Two general approaches may be considered in assessing the long-term health effects of the Chernobyl accident. The first approach is to use risks estimated from other radiation exposure experiences, for example, those of the survivors of the atomic-bomb explosions over Hiroshima and Nagasaki, applied to the doses received by Chernobyl-affected populations and, thus, to estimate the subsequent risks to these populations. The other approach is to conduct empirical studies among Chernobyl-affected populations to assess health effects directly in these populations. These approaches have different advantages and disadvantages. The first approach, often called the risk-projection approach, is usually based on studies of populations with higher doses than experienced by Chernobyl-affected populations and has the advantage of greater statistical power to detect effects and correspondingly narrower confidence intervals around risk estimates. The main disadvantage of this approach is that it involves extrapolation from one exposed population to another in factors such as magnitude of dose, dose rate, genetic composition of the affected population, etc. On the other hand, the empirical approach generally has lower statistical power because of the relatively lower doses experienced by Chernobyl-affected populations (with the exception of thyroid doses), but has the advantage of not usually involving extrapolation.

This report focuses on empirical studies, i.e., those carried out directly in the Chernobyl-affected populations; however, consideration is given, where appropriate, to risks predicted from experiences in other radiation-exposed populations. The empirical studies concerned are epidemiological studies conducted in Belarus, the Russian Federation and Ukraine, since these provide the most direct and convincing evidence of long-term health effects in humans. However, it must be emphasized that the contributions to these epidemiological studies from disciplines such as dosimetry, clinical medicine, genetics and pathology are equally essential in conducting and interpreting such studies correctly. Other studies, e.g., animal experimentation may help in understanding phenomena observed in epidemiological studies and, again, are referred to where appropriate.

Observational epidemiological studies can be broadly classified as ecological, case-control or cohort in design (Rothman and Greenland, 1998a; 1998b). Studies of all three types have the potential to contribute to an understanding of the risk of various diseases after the Chernobyl accident. For all study types, it is essential that there be adequate statistical power to detect the strength of the association of interest.

In ecological studies, sometimes called correlation or aggregate studies, the units of observation are groups of people. Ecological studies have a number of advantages. They are relatively easy, quick and inexpensive, can document the occurrence of disease over time, typically include a large number of cases, and often suggest ideas for subsequent analytical studies. For example, many published studies of thyroid cancer following the Chernobyl accident to date have been ecological (Goulko et al., 1998; Jacob et al., 1999; 2000; Likhtarev et al., 1995; Shakhtarin et al., 2003; Sobolev et al., 1997; Stsjazhko et al., 1995). The most informative ecological studies are those which exhibit the following characteristics: the absence of, or adequate control for, any strong confounding factors, inclusion of areas with sufficient numbers of dose measurements, small variability in dose within the geographical units of study relative to variability across the units, and the availability of health data of uniformly high quality across geographical units. Furthermore, the populations should be relatively stable, to ensure that disease rates largely reflect exposures received in their respective geographical regions.

In addition to ecological studies, various Chernobyl-related case-control and cohort studies are currently in progress. The major advantage of these types of studies is that data are obtained on individuals, enabling calculation of more reliable quantitative risk estimates. Moreover, data on potential confounding factors can be collected and used in the analysis of risk. Of the two analytic study designs, case-control studies can generally be completed in a shorter period of time. Care must be taken, however, to guard against biases that can occur due to the retrospective nature of the design. For case-control studies, important issues are a clear case definition, an appropriate selection of controls, a high response rate among both cases and controls, control for surveillance biases, and a valid retrospective ascertainment of dose that is not influenced by case-control status.

Cohort studies are prospective in nature, following all subjects forward in time. This feature makes cohort studies less susceptible to bias from poor and differential recall. With the cohort design it is possible to study the occurrence of disease over time as well as multiple disease endpoints in the same study. However, cohort studies generally require a longer period of time to carry out, a larger number of study subjects, and therefore, are generally more costly. The most critical elements of a good cohort study are the retention of cohort members through the period of follow-up, uniformity of study procedures over time and across the dose range, good exposure assessment and complete ascertainment of study endpoints.

Chapter 2

DOSIMETRY

Thyroid Dosimetry

There are four components in the thyroid doses resulting from the Chernobyl accident:

1) the dose from internal irradiation resulting from intakes of ^{131}I;
2) the dose from internal irradiation resulting from intakes of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and of short-lived radiotelluriums (^{131}Te and ^{132}Te);
3) the dose from external irradiation resulting from the deposition of radionuclides on the ground and other materials; and
4) the dose from internal irradiation resulting from intakes of long-lived radionuclides such as ^{134}Cs and ^{137}Cs.

For most individuals, the dose from internal irradiation resulting from intakes of ^{131}I is by far the most important and has received almost all of the attention. The dose from ^{131}I was mainly due to the consumption of fresh cow's milk; children on average received a dose that was much greater than that received by adults, because of their small thyroid volume and a consumption rate of fresh cow's milk that was similar to that of adults.

For the purposes of epidemiological studies and risk estimation, it is very important to assess the thyroid doses with a reasonable degree of reliability and to quantify as well as possible the uncertainties attached to the dose estimates. The strengths and weaknesses of the knowledge in those areas are presented below.

Methodologies

The methodologies of estimation of the four components of the thyroid dose will be presented in turn.

Internal irradiation resulting from intakes of ^{131}I

The assessment of the thyroid doses resulting from the intakes of ^{131}I is based on the results of measurements of external gamma radiation performed by means of radiation detectors placed against the neck. Within a few weeks following the accident, approximately 350,000 of those measurements (called "direct thyroid measurements") were made in Belarus, Ukraine, and Russia (Gavrilin et al., 1999; Likhtarev et al., 1996; UNSCEAR, 2000; Zvonova and Balonov, 1993). Usually, individuals were only measured once, so that only the thyroid dose rate at the time of the measurement can be readily derived from the direct thyroid measurement. To calculate the thyroid dose, the variation with time of the thyroid dose rate needs to be assessed. This is done by calculation, taking into account the relative rate of intake of ^{131}I, both before and after the direct thyroid measurement, and the metabolism of ^{131}I in the body, which may have been affected by iodine blocking. For most individuals, the main source of intake of ^{131}I was due to the consumption of contaminated milk, milk products, and leafy vegetables; the inhalation pathway played a substantial role only when contaminated foodstuffs were not consumed.

For the individuals who were not measured but who lived in areas where many persons had been measured, the thyroid doses are reconstructed on the basis of the statistical distribution of the thyroid doses estimated for the people with measurements, together with the knowledge of the dietary habits of the individuals who are considered. Finally, the thyroid doses for people who lived in areas with very few or no direct thyroid measurements within a few weeks after the accident are reconstructed by means of relationships using available data on ^{131}I or ^{137}Cs deposition, exposure rates, or concentrations of ^{131}I in milk (UNSCEAR, 2000; Balonov et al., 2000; Likhtarev et al., 2003; Zvonova et al., 2000). In Belarus, a radioecological model was developed for the assessment of thyroid doses for those people for whom ^{131}I measurements were not available (Kruk, Prohl, and Kenigsberg, 2004). The model, taking into account region-specific contamination data, allowed wide-scale thyroid dose reconstruction for the population of Belarus. The average thyroid doses were estimated for more than 9.5 million persons broken down according to age group (18 one-year age groups for 2,403,317 children and adolescents and one age group for 6,929,109 adults) residing in 23,325 settlements at the time of the Chernobyl accident (Kenigsberg and Kruk, 2004b).

For the subjects who were exposed *in utero*, the estimation of the thyroid dose consists of two steps: 1) estimation of the intake of ^{131}I by the mother (or of the ^{131}I activity in the thyroid if a direct thyroid measurement was performed on her) and 2) estimation of the transfer of ^{131}I from the mother to the fetus (Zvonova, 1998).

In analytical epidemiological studies, personal interviews are used to obtain information on residence history and dietary habits, and on whether the subjects took stable iodine for the purpose of thyroid blockade. In ecological studies, this information is based on the available knowledge for the population that is considered.

Internal irradiation resulting from intakes of short-lived radioiodines and radiotelluriums

The thyroid doses resulting from intakes of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and of short-lived radiotelluriums (^{131}Te and ^{132}Te) are usually estimated using information on the ratios of the radionuclides in the amounts released, or present in the environment, and in man, relative to ^{131}I. The simplest methodology consists in using the estimated radionuclide releases, relative to ^{131}I, and to take into account the time necessary for the radioactive cloud to reach the populated areas of interest to obtain the relative concentrations of the short-lived radionuclides in ground-level air. This allows an estimation of the activities deposited on the ground, the concentrations in foodstuffs, the intakes by humans, and, ultimately, the thyroid doses resulting from those intakes. Only a few measurements were made of the activities in the air (Nedvekaite et al., 2004), deposited on the ground (Makhonko, 1996), or in human thyroids (Balonov et al., 2003).

External irradiation resulting from the deposition of radionuclides on the ground and other materials

External exposure of the population after the Chernobyl accident was mainly due to deposition of gamma-emitting radionuclides, including ^{95}Zr-Nb, ^{131}I, ^{132}Te-I, ^{134}Cs, ^{137}Cs, and ^{140}Ba-La. Because ^{137}Cs was most commonly measured throughout the contaminated zones, deposition densities of the other radionuclides have generally been related to that for ^{137}Cs. Models of radiation transport are used to derive the exposure rates outdoors over open undisturbed terrain from the measured or assumed radionuclide mix deposited on the ground (Muck et al., 2002; Golikov, Balonov, and Jacob, 2002).

The assessment of absorbed doses from external radiation sources requires knowledge of several factors that influence the dose estimates. These factors include: the isotopic composition of the deposited radioactive fallout; whether the deposition was primarily due to wet or dry processes; the soil density and the rates of radionuclide migration into the soil; information about the subject's residence location and lifestyle; and information about the type of dwelling and the settlement in which it was located.

Typically, the external exposure rates at outdoor locations in a settlement are lower than those over open undisturbed terrain. This fact is accounted for through an empirical dose rate reduction factor. External radiation doses to members of the public are further reduced by shielding provided by dwellings and other buildings. A dimensionless shielding factor accounts for the reduction of dose due to time spent indoors in a residence and seasonal variations of exposure rate.

Internal irradiation resulting from intakes of long-lived radionuclides

The deposition of radionuclides onto pastures and other vegetation also led to thyroid doses from internal irradiation. The thyroid doses resulting from intakes of ^{131}I are discussed above. Among the other radionuclides, only the long-lived radioactive isotopes of cesium (^{134}Cs and ^{137}Cs) contributed significantly to the thyroid doses. During the first few weeks after the accident, edible herbs and green vegetables were contaminated directly, and indirect contamination of milk and meat also occurred. The time history of the initial radionuclide ingestion was dependent upon the retention of deposited radionuclides by forage, with a half-time of about two weeks (Prohl et al., 2002).

At later times, doses from intakes of ^{134}Cs declined due to physical decay, and the contribution of ^{137}Cs became an increasing fraction of the total. The intakes of ^{137}Cs and the body burdens of inhabitants of contaminated territories depend on agricultural and radioecological conditions of the region, on the migration and sorption processes of radionuclides in soil, and on the transfer of radionuclides to foodstuffs. For a significant fraction of the exposed populations, consumption of locally produced milk was the most important pathway for radiocesium ingestion (Minenko, Drozdovich, and Tretyakevich, 1996; Likhtarev et al., 2002; Travnikova et al., 2004). The radiocesium transport in a region can be characterized by the soil-to-milk transfer factor, defined as the quotient of the concentration of ^{137}Cs in locally produced milk (Bq L^{-1}) to the deposition density of that radionuclide in soil (kBq m^{-2}). This transfer factor, which depends on the type of soil and agricultural practices, was derived from measurements of ^{137}Cs in soil and milk.

The estimation of the thyroid doses resulting from intakes of ^{134}Cs and ^{137}Cs is essentially based on the numerous measurements of radiocesiums in the body and in milk (Balonov et al., 1995; Minenko et al., 1996; 2004; Likhtarev et al., 2002).

Expert assessment

Consensus

Strengths and weaknesses of methods to estimate thyroid doses from ^{131}I. Thyroid doses from ^{131}I are relatively well known, as they are based on the large number of direct thyroid measurements performed in the contaminated areas of Belarus, Russia, and Ukraine. Environmental and metabolic models, simulating the behaviour of ^{131}I in the environment and of the content of ^{131}I in the thyroid, are also necessary to estimate the relative variation with time, both before and after the direct thyroid measurement. The reliability of the ^{131}I thyroid doses for individuals depends mainly on whether the individual considered had a direct thyroid measurement and on the extent of the available information on his or her residence history and dietary habits during the first two months after the accident.

From the viewpoint of epidemiology, there are different types of thyroid dose:

- doses to specific individuals (called "individual" doses), which are needed for analytical epidemiological studies. The most reliable individual thyroid doses are those derived from direct thyroid measurements on these individuals, and that make use of personal information on residential history and dietary habits obtained during interviews. Thyroid dose estimates were obtained in this manner for the approximately 25,000 cohort members of two epidemiological studies conducted in Belarus and in Ukraine (Likhtarev et al., 2003); the distribution of the thyroid doses is similar in the two countries, with medians of about 0.3 Gy, and a substantial fraction of doses exceeding 1 Gy (Table 1);
- less reliable individual thyroid doses, obtained in case-control studies, in which a large number of subjects did not have a direct thyroid measurement. Personal information on the residential history and dietary habits of the subjects is obtained during interviews that took place some years after the accident and are susceptible to recollection bias;
- in ecological studies, it is sufficient to have doses to unspecified individuals (called "group" doses), who are representative of the average dose received by the members of the group of a given age living in a specified area (settlement, *raion*, or part of oblast). For example, in Russia, an official method of reconstruction of average thyroid dose in a settlement has been accepted (Balonov et al., 2000); Zvonova et al., 2000). Using this method, average thyroid doses were calculated for six age groups in more than 3500 settlements of the four most contaminated regions of Russia: Bryansk, Tula, Orel, and Kaluga. They were published as a reference book of average thyroid dose (Balonov and Zvonova, Eds., 2002) and are used now for ecological epidemiological studies in Russia. A similar catalogue of thyroid dose estimates is also available for the exposed populations of Ukraine. Information on group thyroid dose estimates for Belarus, Russia, and Ukraine was compiled by UNSCEAR (2000).

Uncertainties in ^{131}I thyroid dose estimates. Extensive efforts have been undertaken to evaluate the uncertainties in the estimates of individual and group thyroid doses that are used in the epidemiological studies. Taking as an example the thyroid dose estimates obtained in the framework of the cohort studies conducted in Belarus and in Ukraine, jointly with the US National Cancer Institute (NCI), the distributions of the uncertainties, expressed as geometric standard deviations, vary from one individual to another and range from 1.6 to more than 5.0 (Likhtarev et al., 2003). The medians of the geometric standard deviations are 1.7 for the Ukrainian subjects and 2.1 for the Belarusian subjects. The results of a sensitivity analysis of the contributions of the various parameters to the uncertainty show that the parameters that account for most of the uncertainty are the thyroid mass and those related to the determination of the content of ^{131}I in the thyroid at the time of the direct thyroid measurement. Because the uncertainties in the direct thyroid measurements are higher for Belarusians than for Ukrainians, the uncertainties in the thyroid dose estimates are, on average, higher for the Belarusian subjects than for Ukrainian subjects. Larger uncertainties would be expected to occur for subjects of case-control studies, in which the number of subjects with direct thyroid measurements is relatively small.

Table 1. Distribution of the Ukrainian and Belarusian cohort subjects according to the geometric mean of their thyroid doses (Likhtarev et al., 2003).

Thyroid dose interval, Gy	Number of subjects	
	Ukraine	Belarus
0 – 0.3	7,589	5,039
0.31-1	3,404	3,438
>1	2,227	3,273
All	13,220	11,750

Influence of iodine deficiency on thyroid doses. Some regions contaminated by the Chernobyl accident have areas of mild to moderate iodine deficiency (Yamashita and Shibata, 1997; Shakhtarin et al., 2003). Iodine supplementation was carried out by special anti-goitre dispensaries in the Gomel and Mogilev regions of Belarus and the Bryansk region of Russia, as part of a state programme to eliminate iodine deficiency, but was terminated approximately ten years before the accident (Astakhova et al., 1998). Knowledge of iodine status at the time of exposure is necessary for better dose assessment: as the level of stable iodine in diet decreases, both the thyroid mass and the fractional uptake of ^{131}I by the thyroid increase. Thus, when thyroid doses are derived from direct thyroid measurements, it is important to adjust the thyroid mass to the level of stable iodine intake.

Importance of blocking the thyroid. In order to efficiently protect against doses from ^{131}I, iodine blockade (or prophylaxis) needs to be conducted before or immediately after exposure to ^{131}I (Ilyin et al., 1972). A good example of the use of iodine prophylaxis occurred in Poland, where the effective administration of stable iodine reduced substantially the thyroid doses from ^{131}I (Nauman, 1999; Krajewski, 1990). Unfortunately, this does not seem to have been the case for large segments of the affected population in the former Soviet Union. Iodine blockade was only applied in a relatively appropriate manner to the recovery operation workers who were offered tablets of stable iodine on their arrival to the Chernobyl site during the first few weeks after the accident (UNSCEAR, 2000), and to some evacuees from the 30-km zone, mainly from Pripyat, who were aware of the risks resulting from exposure to ^{131}I (Goulko et al., 1996). It is estimated that the intake of stable iodine tablets during the first 6–30 hours after the accident reduced the thyroid dose of the residents of Pripyat by a factor of 6 on average, and that the combination of stable iodine blockade and being at home resulted in a dose reduction by a factor of approximately 10 (Balonov et al., 2003).

Estimation of in utero doses from ^{131}I. The thyroid doses received *in utero* vary substantially with the stage of pregnancy, but are always smaller than the doses received by infants (Berkovski, 1999a; 1999b; ICRP, 2001; Johnson, 1982; Zvonova, 1998). The thyroid, which begins to be formed during the 12^{th} week of pregnancy, increases in size until the end of the period of gestation. The fractional uptake of iodine by the thyroid also increases during this period. Measurements of thyroid uptake of iodine during the last trimester of gestation are not available.

Estimation of doses from ^{131}I received by recovery operations workers. Because of the abundance of ^{131}I and of shorter-lived radioiodines in the environment of the reactor during the early phase of the accident, recovery operation workers on the site during the first few weeks after the accident may have received substantial thyroid doses from internal irradiation. Most of the liquidators lived in camps, and consumed foodstuffs that were not contaminated. Their thyroid doses were mainly due to external exposure and inhalation of radioiodines during the first few days after the accident. However, many Belarusian liquidators lived at home, so that they were exposed to ^{131}I through inhalation during the non-working hours, and also to ingestion of contaminated foodstuffs at home. Because the clean-up operations lasted more than 4 years, with a rapid turnover of workers and exposure to ^{131}I occurring only during the first two months after the accident, only a relatively small number of recovery operation workers may have been substantially exposed to ^{131}I.

Thyroid doses from short-lived radioiodines. Although the largest contribution to the thyroid dose resulted from intakes of ^{131}I, it is also important to take the short-lived radioiodines and radiotelluriums into consideration because of the suspicion that short-lived radionuclides are more effective for thyroid cancer induction than ^{131}I (NCRP, 1985). Among members of the public, the highest numbers with thyroid doses from short-lived radionuclides, and from ^{131}I, is expected from among the residents of Pripyat, who were evacuated a short time after the accident and who were exposed to radioiodines and radiotelluriums via inhalation only. From an analysis of direct thyroid and lung measurements performed on 65 Pripyat evacuees, the contribution of short-lived radionuclides to the thyroid dose is about 20% for persons who did not employ stable iodine (KI) to block their thyroids and more than 50% for persons who took KI tablets soon after the accident (Balonov et al., 2003). The total thyroid dose among the Pripyat evacuees, however, was relatively small because of the short time of exposure.

For the populations that were not evacuated within a few days after the accident, short-lived radionuclides in general played a minor role, as most of the thyroid exposure resulted from the consumption of contaminated milk and other foodstuffs; for these populations the contribution of the short-lived radioiodines and radiotelluriums is estimated to have been about 1% of the ^{131}I thyroid dose (Gavrilin et al., 2004).

Thyroid doses from external irradiation. External exposure of the population after the Chernobyl accident was mainly due to deposition of the gamma-emitting radionuclides ^{132}Te, ^{131,132}I, ^{140}Ba, ^{140}La, ^{95}Zr, ^{95}Nb, ^{99}Mo, ^{103,106}Ru, ^{141,144}Ce, and ^{134,136,137}Cs. Because ^{137}Cs was most commonly measured throughout the contaminated zones, deposition densities of the other radionuclides have generally been related to that for ^{137}Cs. For children at the time of the accident, the accumulated dose from external irradiation over 15 years is estimated to represent less than 10% of the thyroid dose due to intakes of ^{131}I that was delivered during the few weeks following the accident; for adults at the time of the accident, the contribution of external irradiation was somewhat higher.

Thyroid doses from internal intake of long-lived radionuclides. A few weeks after the accident, following the decay of ^{131}I, ingestion of radiocaesium contained in locally produced foodstuffs became the main pathway of internal exposure. Thyroid doses from ingestion of ^{134}Cs and ^{137}Cs are mainly due to the consumption of root vegetable, the uptake of which depends on the type of soil on which the deposition occurred. Thyroid doses from internal irradiation resulting from intakes of long-lived radionuclides are estimated to represent a few percent of the thyroid dose due to intakes of ^{131}I (Zvonova, 2003; Cardis et al., 2005; Minenko et al., 2004).

Gaps in knowledge

Methods to estimate thyroid doses from ^{131}I. Methods to estimate the thyroid doses use similar concepts, but are different in Belarus, Russia, and Ukraine. The methods are basically of two types – semi-empirical and environmental-transfer based – so that it would be very difficult to merge them in order to develop a joint method. However, the results of limited inter-comparison studies (Khrouch et al., 2004) show that the methods used in Belarus, Russia, and Ukraine are in reasonably good agreement, except in low-contaminated areas.

Although a large number of radiation measurements are available, there are areas where measurements are lacking, so that interpolation methods need to be applied to fill in the gaps.

Uncertainties in estimates of thyroid doses from ^{131}I. The possible correlations between the various parameters that are used in the models have so far received little attention.

Uncertainties in important parameters, such as the thyroid mass, are based on information found in western literature, while the relevant measurements made in the former Soviet Union are largely ignored.

From a systematic comparison of the parameter values and of their assigned uncertainties in the models currently used it would be very helpful to reveal inconsistencies or lack of agreement for certain parameters. Limited work on this has been performed in the study conducted by IARC (Khrouch et al., 2004).

With respect to the estimation of individual thyroid doses, the reliability of responses to personal interviews on residence history or milk consumption rates are not well established.

Influence of iodine deficiency. Published results (Zvonova, 1989) indicate that, for adults, the thyroid dose estimates are roughly independent of the level of stable iodine intake, as the variation in thyroid uptake is compensated by the variation in the thyroid mass. For this reason, the models of thyroid dose estimation that have been applied so far use the reference values recommended by the ICRP, irrespective of the level of stable iodine in the diet. In any case, information on the level of stable iodine intake in the diet of people living in the contaminated areas in 1986 is rather sketchy and somewhat inconsistent.

It is important to note that the available data on the relationship between the thyroid dose from ^{131}I and the level of stable iodine intake in diet refer only to adults; information for children is lacking.

Role of iodine blockage. All measurements of fractional uptake of ^{131}I by the thyroid as a function of stable iodine intake for the purposes of thyroid blocking were made on adults. Information on dietary intakes of stable iodine for children is lacking.

Estimation of in utero doses from ^{131}I. In most Chernobyl studies, the *in utero* doses have been estimated using a model published by Johnson in 1982 (Johnson, 1982) that is based on scarce human data. Recently, Berkovski (1999a; 1999b) published a model that makes use of animal as well as human data; Berkovski's model, which has been adopted by ICRP (2001), leads to thyroid dose estimates that differ substantially from those obtained using Johnson's model for fetuses exposed during the last 2 months of pregnancy. It is not clear whether the fetal thyroid dose increases or decreases during the final months of pregnancy.

The uncertainties attached to *in utero* thyroid dose estimates have received very little attention.

Estimation of doses from ^{131}I received by the recovery operations workers. Information on the thyroid doses of the recovery operation workers is very limited and imprecise (Khrouch et al., 1988; Krjutchkov et al., 1996).

Thyroid doses from short-lived radioiodines. There are only a few measurements from which information on the thyroid dose from short-lived radioiodines and radiotelluriums can be derived. Consequently there are large uncertainties.

Intercomparison of methods. An intercomparison of the methods and parameter values used in Belarus, Russia, and Ukraine to estimate doses from external irradiation received by residents of contaminated areas has not been carried out in a systematic manner. However, limited studies are on-going.

Estimation of thyroid doses from other radionuclides and pathways. An inter-comparison of the methods and parameter values used in Belarus, Russia, and Ukraine to estimate internal doses from ^{134}Cs and ^{137}Cs received by residents of contaminated areas has not been carried out in a systematic manner; however, limited studies are on-going.

Conclusions

Methods to estimate thyroid doses from ^{131}I. The assessment of thyroid doses resulting from the intakes of ^{131}I is based on the results of measurements of external gamma radiation performed using radiation detectors placed against the neck. Within a few weeks following the accident, approximately 350,000 of those measurements (called "direct thyroid measurements") were made in Belarus, Ukraine, and Russia. Considerable efforts have been made to develop reliable thyroid dose estimates from intakes of ^{131}I. The methods of thyroid dose estimation used in the three countries use similar concepts, but are different, and it would be difficult to merge them in order to develop a common method.

Uncertainties in estimates of thyroid dose from ^{131}I. Extensive efforts have been undertaken to evaluate the uncertainties in the estimates of individual and group thyroid doses that are used in epidemiological studies. Much work remains to be done to assess the uncertainties in a consistent and less subjective manner in the three countries.

Influence of iodine deficiency. Some of the contaminated areas of Belarus, Russia, and Ukraine are also areas of mild or moderate iodine deficiency. As the level of stable iodine in the diet decreases, both the thyroid mass and the fractional uptake of ^{131}I by the thyroid increase. When thyroid doses are derived from direct thyroid measurements, it is important to adjust the thyroid mass to the level of stable iodine intake. When thyroid doses are derived from intakes of ^{131}I, the assumption is generally made that the dose is independent of the level of iodine deficiency.

Role of iodine blockage. In order to protect efficiently against doses from ^{131}I, iodine blockage needs to be conducted before or immediately after exposure to ^{131}I. It is estimated that the intake of stable iodine pills during the first 6–30 hours after the accident reduced the thyroid dose of the residents of Pripyat, who were evacuated the day after the accident, by a factor of 6 on average and that the combination of stable iodine blockage and being at home resulted in a dose reduction by a factor of approximately 10.

Estimation of in utero doses from ^{131}I. The thyroid doses received *in utero* vary substantially with the stage of pregnancy, but are in any case smaller than the doses received by infants. The available models to estimate thyroid doses received *in utero* are in reasonable agreement for the fetus during the first six months of gestation, but there are discrepancies for the last trimester of gestation. The uncertainties attached to the *in utero* thyroid dose estimates have so far received very little attention.

Estimation of thyroid doses from other radionuclides and pathways. Although the intake of ^{131}I is usually by far the most important contributor to the thyroid dose, there are other components in the thyroid doses resulting from the Chernobyl accident:
1) the dose from internal irradiation resulting from intakes of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and of short-lived radiotelluriums (^{131m}Te and ^{132}Te);

2) the dose from external irradiation resulting from the deposition of radionuclides on the ground and other materials; and
3) the dose from internal irradiation resulting from intakes of long-lived radionuclides such as ^{134}Cs and ^{137}Cs.
The thyroid doses from these radionuclides and pathways represent, for most individuals, a small percentage of the thyroid dose due to ^{131}I.

Recommendations

Methods of evaluation. Extensive inter-comparison exercises, especially for populations living near the borders of the affected states, should be organized to make sure that the methods of thyroid dose estimation from intakes of ^{131}I yield consistent results. Efforts should also be made to develop common methods that could be applied to the affected populations in Belarus, Russia, and Ukraine.

Uncertainties in dose estimates. Further work on the evaluation of uncertainties in thyroid dose estimates is strongly encouraged. This should lead to the determination of parameters that give rise to the highest uncertainties and to research aimed at reducing those uncertainties. Cooperation and exchange of information among the dosimetrists from Belarus, Russia, and Ukraine working in that area are also strongly encouraged.

Influence of iodine deficiency. Substantial work remains to be done to relate the values of thyroid uptake and thyroid mass to the level of stable iodine intake. It is recommended that a thorough review be made of all published and unpublished data, especially for children to better determine the influence of iodine deficiency on thyroid dose..

Role of iodine blockage. The main recommendation is to educate health care providers on the proper use of potassium iodide (KI) in order to reduce the dose from ^{131}I in case of a reactor accident. Research should be conducted to assess the effectiveness of the administration of stable iodine for thyroid blocking purposes in children.

Estimation of in utero doses from ^{131}I. Research should be conducted to perform a careful estimation of the uncertainties in *in utero* thyroid dose estimates.

Estimation of thyroid doses from other radionuclides and pathways. Even though the thyroid doses from other radionuclides and pathways represent, for most individuals, a small percentage of the thyroid dose due to ^{131}I, it would be useful to conduct an inter-comparison of the methods and parameter values used in Belarus, Russia, and Ukraine to estimate the contributions that these radionuclides and pathways make to the thyroid dose.

Whole-Body and Non-Thyroid Specific Organ Dosimetry

Four groups of exposed individuals are of interest: the recovery operation workers, the evacuees in 1986, those resettled after 1986, and residents in the contaminated territories.

The recovery operation workers were mainly exposed to external irradiation arising from the contamination of the site by radioactive materials. The radiation exposures of members of the public resulting from the Chernobyl accident were due initially to ^{131}I and short-lived radionuclides and subsequently to radiocaesiums (^{134}Cs and ^{137}Cs) from both external irradiation and the consumption of foods contaminated with these radionuclides. The doses received by the recovery operation workers and by the general population are considered below.

The emphasis is on doses relevant to the possible induction of leukaemia and solid cancers other than thyroid cancer, i.e., whole-body doses, bone-marrow doses and doses to other individual organs other than the thyroid. The dosimetry relevant to the thyroid gland was covered in the previous section above.

Doses to recovery operation workers

Current methodologies. The workers involved in the accident can be divided into two groups: 1) the emergency workers, who were involved in fire fighting and other emergency measures during the first day of the accident (26 April 1986), and 2) the recovery operation workers, who were active in 1986-1990 at the power station or in the zone surrounding it for decontamination work, sarcophagus construction, other recovery operation activities, and the operation of other units of the nuclear power plant.

The emergency workers, who received very high doses, resulting for a number of them in a diagnosis of acute radiation sickness, are not considered in this report. Their doses were estimated mainly by means of clinical dosimetry methods, i.e., on the basis of blood formula and/or cytogenetic parameters of blood lymphocytes (UNSCEAR, 2000); these methods are applicable to small numbers of human subjects and not for large-scale epidemiological studies.

For the recovery operation workers, estimates of doses from external gamma irradiation could be obtained either at the time of exposure or retrospectively. At the time of exposure, the following methods were used:
1) individual dosimetry for atomic energy workers and a small number of the military personnel after June 1986;
2) group dosimetry (an individual dosimeter was assigned to one member of a group of recovery operation workers assigned to perform a particular task, and all members of the group were assumed to receive the same dose); and
3) group assessment method (dose to the whole group of liquidators was assessed by a dosimetrist in advance with respect to the dose rate at the work location and planned duration of work).
Methods of retrospective dose estimation include:
4) time-and-motion studies (measurements of gamma-radiation levels were made at various points of the reactor site, and an individual's dose was estimated as a function of the points where he or she worked and the time spent in these places), and
5) biodosimetry (Electron Paramagnetic Resonance (EPR) measurements on teeth, or Fluorescence In-Situ Hybridization (FISH) measurements on blood lymphocytes).
Methods 2 and 3, or their combination, were used for the majority of military personnel at all times. So far, method 5 has only been used for validation purposes on a limited number of workers.

The main sources of uncertainty associated with the different methods of dose estimation are as follows:

- individual dosimetry (method 1): incorrect use of the dosimeters (inadvertent or deliberate actions leading to either an overexposure or an underexposure of the dosimeters);
- group dosimetry (methods 2 and 3): very high gradient of exposure rate at working places at the reactor site;
- time-and-motion studies (method 4): deficiencies in data on itineraries and time spent at the various working places combined with uncertainties in the exposure rates. A high degree of conservatism was used in the early applications of the method;
- biodosimetry (method 5): a relatively high background, which prevents low doses from being measured with reliability, and a lack of knowledge as to other sources of radiation exposure.

Uncertainties associated with the different methods of dose estimation have been assessed to be up to 50% for method 1 (if the dosimeter was correctly used), up to a factor of 3 for method 2, and up to a factor of 5 for methods 3 and 4 (Pitkevich et al., 1997). Uncertainty of the EPR dosimetry (method 5) can be assessed by the following model: absolute term of uncertainty in the low-dose range (below 250 mGy) is 25 mGy (one sigma), and a relative error in the higher dose range (above 250 mGy) – about 10% (Chumak et al., 2005).

In addition to whole-body doses from external gamma irradiation, recovery operation workers received doses from external beta irradiation to the skin and to the lens of the eye, as well as thyroid and whole-body doses from internal irradiation. The dose to unprotected skin from beta exposures is estimated to have been several times greater than the gamma dose. Ratios of dose rates of total exposures (beta + gamma) to gamma exposures, measured at the level of the face, ranged from 2.5 to 11 (average, around 5) for general decontamination work and from 7 to 50 (average, 28) for decontamination of the central hall of the Unit 3 reactor (Osanov, Krjutchkov, and Shaks, 1993). It is worth noting that most of the skin was shielded by clothes and that the beta dose to protected skin was much smaller than the dose to unprotected skin. The problem of beta dose assessment to eye lens was addressed by the Ukrainian-American Chernobyl Ocular Study, which is a cohort study of cataract among 8,607 Ukrainian recovery operation workers. The assessment of the beta dose was derived from the gamma exposure of the subjects. Gamma-to-beta dose conversion coefficients were calculated using Monte-Carlo procedures for a variety of beta emitter spectra and conditions of exposure. Preliminary findings showed that the distribution of individual beta/gamma ratios was quite broad (Chumak, 2005).

The internal doses resulting from intakes of radionuclides such as ^{90}Sr, ^{137}Cs, ^{239}Pu, and others have been assessed for about 300 recovery operation workers, who were monitored from June to September 1986. The majority of them were staff of the Chernobyl power plant, who took part in the recovery work starting on days 3 and 4 after the accident. They were selected for study on the basis of their high levels of external exposure. Dose assessment was based on the analysis of whole-body measurements and radionuclide concentrations in excreta. The average value of the effective dose committed by the radionuclide intakes was estimated on the basis of ICRP Publication 30 to be 85 mSv (ICRP, 1979).

The registries of the national dose data of Belarus, Russia, and Ukraine, presented in Table 2, show that the number of recovery operation workers and the average recorded doses (from external irradiation only) decreased from year to year, with a mean dose of about 130 mGy in 1986. The decrease in recorded doses reflects the decrease in the dose limits, which, for most workers, were 250 mGy in 1986, 100 mGy in 1987, and 50 mGy in 1988 and in later years. The percentage of recovery operation workers with recorded dose follows the reverse tendency: it is low in 1986 and 1987, when the doses were relatively high, and it is higher in 1988-1989, when the doses were lower. Although the doses presented in Table 2 provide an indication of the exposures, they are not to be relied upon without further analysis because of the biases introduced by some of the methods of dose estimation and the falsification of data that may have occurred for a small percentage of workers (Chumak et al., 2000).

Table 2. Distribution of external doses to recovery operation workers as recorded in national registries (Kenigsberg and Kruk, 2004a; Ministry of Health of Ukraine, 1999; Cardis and Okeanov, 1996).

Country and period	Number of recovery operation workers	Percentage for whom dose is known	External dose[a] (mGy)			
			Mean	Median	75th percent-tile	95th percent-tile
Belarus						
1986	68 000	8	60	53	93	138
1987	17 000	12	28	19	29	54
1988	4 000	20	20	11	31	93
1989	2 000	16	20	15	30	42
1986-1989	91 000	9	46	25	70	125
Russian Federation						
1986	69 000	51	169	194	220	250
1987	53 000	71	92	92	100	208
1988	20 500	83	34	26	45	94
1989	6 000	73	32	30	48	52
1986-1989	148 000	63	107	92	180	240
Ukraine						
1986	98 000	41	185	190	237	326
1987	43 000	72	112	105	142	236
1988	18 000	79	47	33	50	134
1989	11 000	86	35	28	42	107
1986-1989	170 000	56	126	112	192	293

[a] The external dose is expressed in mGy for reader's convenience. In fact, the quantity measured was, in many cases, exposure and not the dose.

For analytical epidemiological studies, the dosimetric information that is required is an estimate of the absorbed dose of interest (bone marrow for blood diseases, breast for breast cancer, etc.) for all individuals enrolled in the study, as well as an assessment of the uncertainty attached to the dose estimate. For that purpose, the registry data need to be supplemented with or replaced by other information, including some obtained during personal interviews. On-going epidemiological studies use a time-and-motion method, called RADRUE (Krjuchkov et al., 2004). This method relies on an accurate knowledge of the radiation field at the locations where the worker was exposed, as well as the whereabouts of the worker, which are obtained by means of personal interviews. Biodosimetry methods can also be used to calibrate the dosimetry results recorded in the Registries or obtained with RADRUE, though at the present time, the accuracy and precision of biodosimetric methods does not allow their use at very low doses. A unique tooth collection network has operated in Ukraine since 1997 and has already yielded about 6,000 tooth samples for use in EPR dosimetry. This network is instrumental in the framework of dosimetry validation studies that had used EPR dosimetry as a reference (Chumak et al., 2005).

Doses to the general population

Current methodologies. The doses received by the members of the general public resulted from the radionuclide releases from the damaged reactor, which led to the ground contamination of large areas. Iodine-131 was the main contributor to the thyroid doses, received mainly via internal irradiation within a few weeks after the accident, while ^{137}Cs was, and is, the main contributor to the doses to organs and tissues other than the thyroid, from either internal or external irradiation, which will continue to be received, at low dose rates for several decades.

Within a few weeks after the accident, more than 100,000 persons were evacuated from the most contaminated areas of Ukraine and Belarus. The thyroid doses received by the evacuees varied according to their age, place of residence, and date of evacuation. For example, for the residents of Pripyat, who were evacuated essentially within 48 hours after the accident, the population-weighted average thyroid dose is estimated to be 0.17 Gy, and to range from 0.07 Gy for adults to 2 Gy for infants. For the entire population of evacuees, the population-weighted average thyroid dose is estimated to be 0.47 Gy. Doses to organs and tissues other than the thyroid were, on average, much smaller (Table 3).

Doses have also been estimated for the approximately 6 million residents of the contaminated areas (defined as being areas where the ^{137}Cs deposition density was greater than 37 kBq m^{-2}) who were not evacuated. Following the first few weeks after the accident, when ^{131}I was the main contributor to the radiation exposures, doses were delivered at much lower dose rates by radionuclides with much longer half-lives. Since 1987, the doses received by the populations from the contaminated areas have resulted mainly from external exposure from ^{134}Cs and ^{137}Cs deposited on the ground and internal exposure due to contamination of foodstuffs by ^{134}Cs and ^{137}Cs. Other, usually minor, contributions to the long-term radiation exposures include the consumption of foodstuffs contaminated with ^{90}Sr and the inhalation of aerosols containing ^{239}Pu. Both external irradiation and internal irradiation due to ^{134}Cs and ^{137}Cs result in relatively uniform doses in all organs and tissues of the body.

Table 3 Summary of estimated thyroid and effective doses to populations of areas evacuated in 1986 (Bennett et al., 2000).

Country	Estimated arithmetic mean dose		
	Thyroid (Gy)	External effective dose (excluding thyroid) (Sv)	Internal effective dose (excluding thyroid) (Sv)
Belarus	1.0	0.03	0.006
Ukraine	0.3	0.02	0.01

Methodologies of dose estimation have been prepared in Belarus, Russia, and Ukraine and applied to the populations of the contaminated areas. Catalogues of average doses in all settlements of the three Republics are available. The average effective doses from ^{134}Cs and ^{137}Cs that were received during the first ten years after the accident by the residents of contaminated areas are estimated to be about 10 mSv (Table 4). This value, however, may vary for different age groups.

Table 4 Summary of estimated average effective doses (excluding thyroid doses) to populations of areas contaminated by the Chernobyl accident (1986-1995) (Bennett et al., 2000).

Country	Estimated arithmetic mean effective dose (mSv)		
	External Exposure	Internal exposure	Total
Belarus	5	3	8
Russian Federation	4	2.5	6.5
Ukraine	5	6	11

The dosimetry information needed in analytical epidemiological studies consists of individual absorbed doses in the tissue of interest for all subjects, as well as estimates of uncertainty. The method currently used to derive the individual dose estimates consists in modifying the average doses provided in the catalogs, using information obtained by means of personal interviews. For external irradiation, the information necessary is the residence history, together with the type of building where the subject worked and resided. For internal irradiation, information on foodstuffs (type, origin, and consumption rates) is needed. In order to estimate or reduce the uncertainties in the individual doses, validation studies have been conducted (Chumak, Likhtarev, and Pavlenko, 1999; Golikov et al., 2002) using personal dosimeters for external irradiation and data on whole-body contents or radionuclide concentrations in foodstuffs (usually milk) for internal irradiation (Balonov et al., 2000).

Expert assessment

Consensus

Doses to recovery operation workers. There are about 200,000 dose estimates in the Registries of recovery operation workers of Belarus, Russia, and Ukraine. In analytical epidemiological studies, doses need to be estimated for all enrolled subjects, whether their doses are recorded in the Registries or not. On-going epidemiological studies use a specific time-and-motion method, called RADRUE (Krjuchkov et al., 2004). In addition, biodosimetry methods are used for validation purposes for a limited number of workers.

Doses to the general population. Methodologies for the estimation of the effective doses in any settlement of the contaminated areas of Belarus, Russia, and Ukraine have been developed and applied to the populations of those settlements. Catalogues of effective doses are available, both for annual doses and for doses accumulated until 1995, 2001, or 2002. Validation studies have been conducted, both for external and for internal irradiation.

Gaps in knowledge

Doses to recovery operation workers. The national registries data are incomplete, as they cover less than half of the total number of recovery operation workers, and do not include information on affiliation or on the type of work carried out on the site.

Doses, as they are recorded in the Chernobyl state Registries of Belarus, Russia and Ukraine, may not always be accurate, thus contributing to the uncertainty in analytical epidemiological studies, in which individual doses have to be estimated. For about 10% of the military workers, the Registry data are thought to have been falsified, and thus to be unreliable (Chumak and Krjuchkov, 1998). For the remainder of the military workers, the doses are systematically overestimated by a factor of about 2 (Ilyin et al., 1995). The registries data need to be supplemented using other information and verified using another method.

Absorbed doses for the organ or tissue of interest in the epidemiological studies are not available in the literature. They remain to be calculated on the basis of limited information on the radiation deposition in various locations and various times after the accident.

Doses from internal irradiation are expected to have been small, when compared to the doses from external irradiation, but they have not been given much attention. Information on doses from beta radiation to the skin and to the lens of the eye also is limited.

There are large uncertainties in the dose estimates obtained by means of the various methods, and it is not clear whether these uncertainties could be reduced substantially. In particular, the influence of recall bias during interviews has not been studied adequately.

Biodosimetry methods (EPR and FISH) have been applied to a limited number of workers, but their application is limited to relatively high doses (50 mGy for EPR and 300 mGy for FISH).

Doses to the general population. There are a number of weaknesses or inadequacies in estimated doses to the general population. Some of the issues identified are as follows: 1) there is a lack of information on intercomparison between the various dosimetric methods, although studies are currently in progress. 2) Doses to be received in the future can only be roughly predicted. 3) The reliability of interviews used to assess factors that affect an individual's dose has not been definitively assessed. 4) Internal doses resulting from intakes of ^{90}Sr and of ^{239}Pu have received limited attention. 5) Methods to estimate doses received by those exposed *in utero* need further work on the dosimetric methodology and validity of such dose estimates. 6) The conversion of effective doses into absorbed organ-specific doses such as bone marrow dose needs to be delineated.

Conclusions

Doses to recovery operation workers. The dose estimates provided in the national Registries should be used with caution. The Registry data need to be supplemented using other information and verified using another method.

The best method currently available to estimate the doses received by the recovery operation workers is a time-and-motion assessment, called RADRUE. One of the main advantages of this method is that it can be applied to any worker.

Doses to the general population. Methodologies for the estimation of the effective doses from ^{134}Cs and ^{137}Cs in any settlement of the contaminated areas of Belarus, Russia, and Ukraine have been developed and applied to the populations of those settlements. These methods can be easily adapted to derive the information needed in analytical epidemiological studied: individual dose estimates and uncertainties.

Recommendations

Doses to recovery operation workers. The RADRUE method, which is applied in the on-going epidemiological studies, should continue to be validated using reliable results obtained by means of other methods. Efforts to quantify and/or to reduce the uncertainties associated with the RADRUE method should be pursued.

Biodosimetry methods should be used to validate the doses recorded in the Registries or obtained by RADRUE. However, efforts should be made to make sure that the biodosimetry methods can be applied reliably to all workers above a certain dose level.

Doses to the general population. Efforts should be made to:
1) intercompare the methods of dose estimation;
2) assess the reliability of the interviews;
3) estimate the doses received *in utero*;
4) derive absorbed doses from the effective doses available in the catalogs, and
5) estimate the doses resulting from intakes of ^{90}Sr and ^{239}Pu.

Chapter 3

THYROID DISEASE

One of the major components of the radionuclides released by the Chernobyl accident was iodine-131 (^{131}I). Fallout of radioactive iodines led to considerable exposure of local residents through inhalation and ingestion of contaminated foodstuffs. The thyroid gland accumulates iodine from the blood stream as part of its normal metabolism. It is known to be one of the most susceptible organs to cancer induction by external x- and gamma radiation (Ron et al., 1995). Children were found to be the most vulnerable population, and a substantial increase in thyroid cancer among those exposed as children was recorded following the accident. Susceptibility of the thyroid to internal exposure from radioactive iodines is less clearly established and quantified (Shore, 1992), and the Chernobyl accident has provided a unique opportunity to further assess this issue. This chapter focuses primarily on thyroid cancer, but other thyroid pathologies, e.g., autoimmune thyroiditis, are also discussed.

Epidemiology

Current status of evidence

The overall number of thyroid cancer cases diagnosed in Belarus, Ukraine and in the four most contaminated regions of Russia during 1986-2002 among those who were children or adolescents (0–17 years) at the time of the Chernobyl accident is presented in Table 5. The reported numbers slightly differ depending on the sources, but there is agreement that the overall number observed in the three countries is above 4000.

Table 5. Number of cases of thyroid cancer diagnosed between 1986 and 2002 by country and age at exposure

Age at exposure (yr)	No of Cases			
	Belarus[1]	Russian Federation[2]	Ukraine[3]	Total
0-14	1 711	349	1 762	3 822
15-17	299	134	582	1015
Total	2 010	483	2 344	4 837

[1] Cancer Registry of Belarus, 2006
[2] Cancer subregistry of the Russian National Medical and Dosimetric Registry, 2006 (for the 4 most contaminated regions)
[3] Cancer Registry of Ukraine, 2006

Epidemiological studies of late health consequences of the Chernobyl accident have mainly focused on thyroid cancer in children, although studies in recovery operation workers and adult residents of contaminated areas have also been conducted (Kesminiene et al., 2002; Moysich, Menezes, Michalek, 2002). To date, the results of the epidemiological studies that became available after 2000 support the conclusions of the UNSCEAR 2000 Report. Reported findings from the most informative descriptive epidemiological studies are summarized in Table 6; findings of recent analytical studies are also presented in the text.

In a descriptive study carried out by Heidenreich et al. (2000), the authors found an increase in the excess absolute risk (EAR) with time since exposure for thyroid cancer in children of Ukraine. Jacob et al. (2000) reported results of the Belarus-Germany study that investigated patterns of childhood thyroid cancer incidence in 1991-1996. The EAR for the Chernobyl birth cohort of 1971-1986 was compared with the EAR from a combined analysis of several cohorts of externally exposed persons (Ron et al., 1995). The point estimate of the EAR per unit of thyroid dose was found to be half of the risk among externally exposed cohorts in the pooled analysis by Ron et al. (1995). However, this difference is not statistically significant. An estimate of the excess number of future thyroid cancer cases was also made in this paper, assuming a constant EAR over time. For Belarus, starting in 1997, the number was estimated to be 15,000 (uncertainty range 5,000–45,000) cases over 50 years. This was estimated to be an increase of about 80% over the baseline rate without radiation exposure, but with screening.
In a thyroid screening study, Shibata et al. (2001) estimated the odds ratios (OR) for thyroid cancer, comparing children born before April 26, 1986, during 1986, and after 1986 with the latter group used as a reference. The OR for those born before April 1986 was found to be 121 (95% CI 9–31,000), and for those born between the accident time and the end of 1986, the OR was 11 (3–176). This approach was used to minimize dosimetry-related uncertainties, although other uncertainties remain, for example, the ratio of maternal to fetal thyroid dose, doses from breastfeeding, and source/amount of maternal milk intake while pregnant or breastfeeding.

Ivanov et al. (2002) reported the results of thyroid cancer incidence analyses in a cohort of liquidators (99,024 persons) living in 6 regions of Russia: North-West, Volgo-Vyatsky, Central-Chernozemny, Povolzhsky, North-Caucasus and Urals. In the period 1986-1998, a total of 58 thyroid cancer cases were detected in this cohort. A statistically significant increase in the thyroid cancer incidence rate was found in liquidators as compared to the baseline (male population of Russia) (SIR 4.33; 95% CI 3.29–5.60), but no dependence of risk on dose from external exposure dose was demonstrated (ERR/Gy -2.23; 95% CI -4.67–0.22). This may be explained by several factors: the influence of the screening effect, the absence of individual internal dose estimates, which may or may not correlate well with the external doses, and the imprecise estimates of external doses.
Ivanov et al. (2003a) reported results of an incidence study in adult residents of the Bryansk region of the Russian Federation. Included were 1051 cancers diagnosed in 1986-1998, including 769 after a presumed 5-year latency period (1991-1998) for radiation. The ratios (SIR) were increased for both pre- and post-latency periods and for both males and females. No increase of the ERR per Gy was estimated. During 1991-1998, 106 cases of thyroid cancer were diagnosed in children of the Bryansk region, and a significant increase over spontaneous incidence was reported in this population during the same period. The SIR for the region was 5.37 (95% CI 4.40–6.49) using national statistics for comparison.

Table 6. Selected results of recent descriptive epidemiological studies of Chernobyl exposure and thyroid cancer, available through *Pub Med* database, as of October 1, 2003.

Study (reference)	Study design and population	Exposure assessment	End points	Results
Thyroid cancer in children – risk and time patterns (Heidenreich et al., 2000)	Ukraine children		EAR	EAR* increased with the time since exposure
Population study on thyroid cancer incidence in Belarus (Jacob et al., 2000)	Belarus children - Chernobyl birth cohort (born at 1986)	Average thyroid doses for age groups in settlements	EAR	Point estimate of EAR per unit of dose was half of the risk in the pooled analysis studies after external exposures
Summary of the 15 year observation of thyroid cancer among Ukrainian children after the Chernobyl accident (Tronko et al., 2002)	Ukraine, children aged <15 at the time of surgery	Average thyroid doses based on residency	Crude incidence rate	Higher incidence rate in heavily contaminated regions correlating with average thyroid exposure dose by settlement
Thyroid cancer in Ukraine children and adolescents following Chernobyl accident (15-year of investigations) (Tronko et al., 2002)	Ukraine, children and adolescents at the time of accident	Average thyroid doses based on residency	Crude Incidence rate	Higher incidence for all age groups in heavily contaminated regions correlating with average thyroid exposure dose by settlement
Thyroid cancer in liquidators of RF (Ivanov et al., 2002)	Russian clean-up workers, 99024 persons	External doses only	SIR ERR/Gy	Increased incidence, not associated with external exposure dose
Thyroid cancer in adolescents and adult residents of Bryansk region (Ivanov et al., 2003a)	Bryansk region residents aged 15-69, about 1,000,000 people	Average thyroid doses for settlement based on State models	SIR ERR	SIR increased, no associated with external dose
School-based thyroid cancer study in Gomel region of Belarus (Shibata et al., 2001)	21601 school-children of Gomel region, Belarus		OR	OR = 121 (95%CI 9-31K) for children born before accident
Population study on thyroid cancer in children of Bryansk oblast of RF (Shakhtarin et al., 2003)	2590 children (6-18) and 480 adults residents of Bryansk oblast		ERR	ERR increased with dose and decreased with urinary iodine excretion

Shakhtarin and colleagues investigated the relationship between iodine-deficiency, thyroid radiation doses and risk of thyroid cancer in young people in the Bryansk region (Shakhtarin et al., 2002; 2003). The excess relative risk (ERR) was significantly associated with increasing thyroid dose, and was inversely associated with urinary iodine excretion levels. In a joint effect of radiation dose and iodine deficiency, the ERR for the territories with severe iodine deficiency was approximately twice that in areas with normal iodine intake, thereby suggesting that iodine deficiency may enhance the risk of thyroid cancer following radiation exposure.

Tronko et al. (2002) reported 1876 cases of thyroid cancer diagnosed in 1986-2000 in Ukrainian children aged 0–18 at the time of exposure. Among those, 70.3% were younger than 15, with the highest increase in incidence among the 0–4 age group. Since 1990 the youngest age group demonstrated a steady rise of thyroid cancer incidence in the exposed cohort.

Tronko et al. (2003) reported results of a descriptive study of the incidence of surgically treated thyroid cancer in Ukrainian children. For the 1986-2000 period, 472 operated patients were age 4–14 at the time of surgery. Most of them were born before the Chernobyl accident. The highest incidence rate was reported in 1996 (0.57 per 100 thousand children aged 0–14) in the six most contaminated regions (Kiev, Chernigov, Zhitomir, Rovno, Cherkassy regions, and the City of Kiev) that was 11.4 times the average pre-Chernobyl incidence rate (0.05) for this age group. The incidence rate in these regions appeared to be associated with higher thyroid doses with the most pronounced effect for doses >0.5 Gy. The pathology results for these cases showed that 92% of all cases included in the study were predominantly represented by solid-follicular subtype of papillary carcinomas, 62% of which involved regional lymph nodes.

In addition to the above studies, which are primarily descriptive in nature, recent analytical studies provide strong evidence of a relationship between radiation dose from the Chernobyl accident and the risk of thyroid cancer in children. Recently completed and ongoing studies are described in Table 7.

The joint Belarus-Russia-IARC-SMHF case-control study of thyroid cancer in young people is a population-based study carried out in the most contaminated regions of Belarus (Gomel and Mogilev) and Russia (Bryansk, Kaluga, Orel and Tula) (Cardis et al., 2002; 2005). The study population was all those living in these regions who were aged 0–14 at the time of the accident in Belarus and 0–18 in Russia. Cases were recruited over the time period 1992-1998. The study included 276 cases and 1300 matched controls aged less than 15 years at the time of the accident. The objectives of the study were to evaluate the risk of thyroid cancer related to exposure to ^{131}I in childhood and adolescence and the role of environmental and host factors that may modify radiation induced thyroid cancer risk. These include age at exposure, stable iodine intake, genetic background and reproductive history. Data collection and verification are complete. The thyroid cancer diagnoses were reviewed by a panel of pathologists. Methods for estimating individual thyroid doses of ^{131}I and short-lived isotopes (and associated uncertainties) were developed and validated. The uncertainties related to the model and to the subjects' responses to the questionnaires are being quantified. Levels of iodine deficiency at the time of the accident and in the years since the accident have been derived through estimation of the area-weighted iodine content in soils around the settlements where study subjects lived.

Table 7. On-going studies of thyroid disease among Chernobyl-affected populations (as of December 2003)

Study	Institution, PI	Collaborating Institutions	Study population	Time-frame
Joint Belarus-Russia-IARC-SMHF case-control study on thyroid cancer in young people	WHO/IARC, E. Cardis, A. Kesminiene and V. Drozdovitch	BelCMT, Minsk; IRME, Minsk; Belarusian Cancer Research Centre, Minsk Gomel Specialized Dispensary, Gomel, Mogilev Diagnostic Centre, Mogilev, IBP, Moscow; MRRC RAMC, Obninsk Institute of Radiation Hygiene, St-Petersburg, Bryansk Diagnostic Centre, Bryansk, Bryansk, Kaluga, Orel and Tula regional centres of the NRMDR University of Pisa, Italy; University of Cambridge, UK University of Nagasaki, Japan US National Cancer Institute, Rockville, MD, USA	BY, RF	Study complete; First paper accepted; supplementary analyses to be carried out in 2005
Case-control study of thyroid cancer among liquidators	WHO/IARC, E. Cardis and A. Kesminiene	BelCMT, Minsk; RIHBT, Minsk; IBP, Moscow; MRRC RAMC, Obninsk Centre of Radiation Medicine, Kiev; Chernobyl Power Plant, Chernobyl Institute of Experimental and Clinical medicine, Tallinn Latvian Cancer Registry, Riga; Lithuanian Cancer Registry, Vilnius IRSN, Fontenay-aux-Roses US National Cancer Institute, Rockville, MD, USA	BY, RF, Lithuania, Latvia, Estonia	Dose reconstruction being completed. Analyses to start in Jan. 2004;underway First paper expected late 2005
A case-control study on thyroid cancer in young people	SMHF, Y. Shibata	Nagasaki University, Japan IARC MRRC RAMS, Obninsk Gomel Specialized Dispensary, Gomel Mogilev Diagnostic Center, Mogilev	BY, RF	Analysis is under progress. Paper in preparation.
Ukraine-Belarus-USA study on childhood thyroid cancer	NCI, M. Hatch, G. Howe	Institute of Endocrinology and Metabolism, Kiev, Ukraine Republican Center of Radiation Medicine and Human Ecology Gomel , Belarus	BY and UA, age <18 years in 1986	Screening initiated in 1998. First results are published in 2003-2004
A case-control study in the Bryansk Oblast, RF	FHCRC, S. Davis	Sloan Kettering MRRC-Obninsk Bryansk Diagnostic Center	RF, Bryansk Oblast	Study complete. Paper published in December 2004

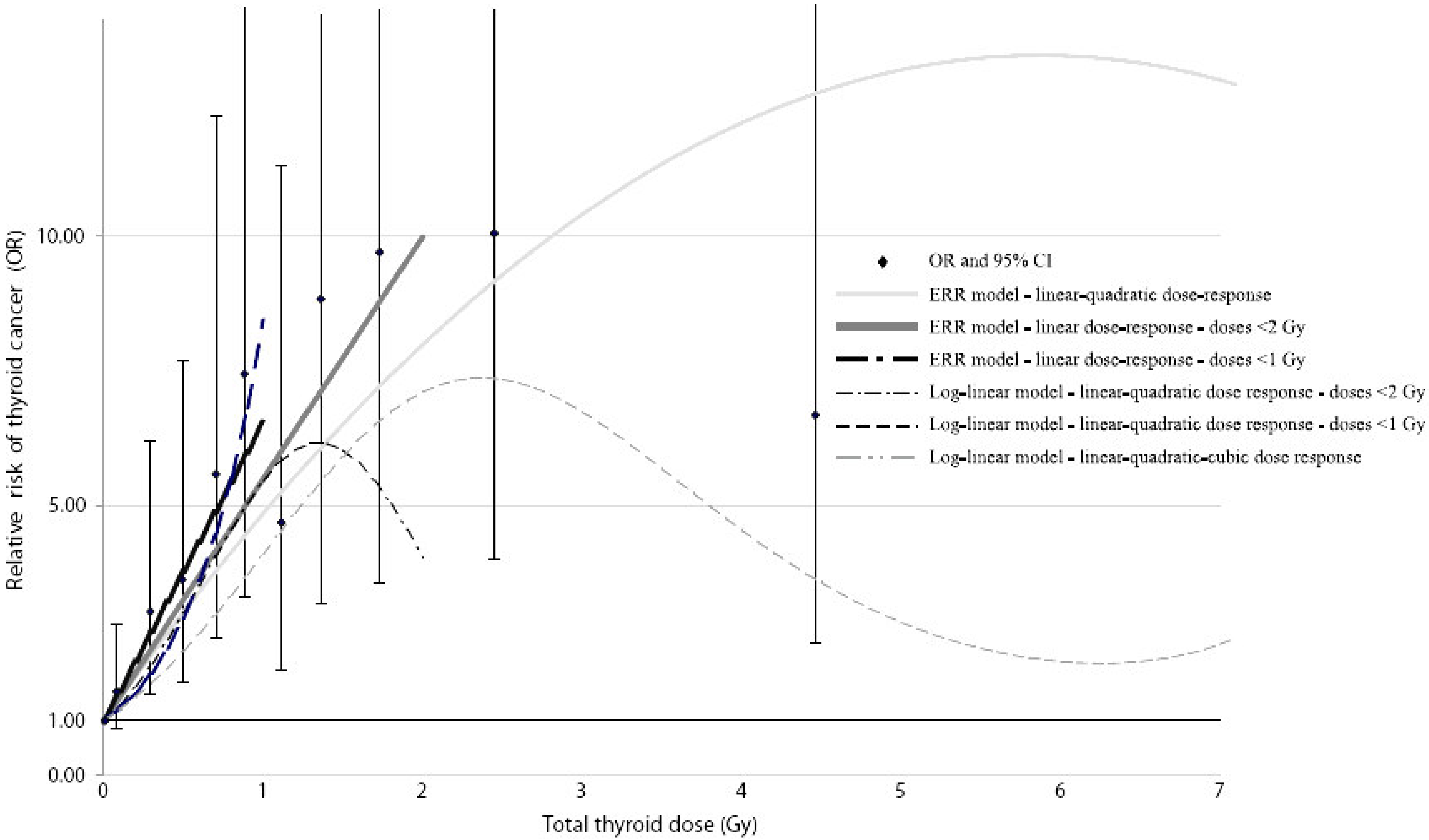

Figure 1. Comparison of relative risks predicted by the different risk models (ERR and log-linear over the entire dose range and in restricted doses ranges) with categorical relative risk estimated in 11 dose categories (from Cardis *et al*, 2005)

A very strong dose-response relationship was observed in this study. Overall, the risk estimate is slightly lower, but similar, to the OR at 1 Gy of 8.7 (95% CI 3.1–9.7) observed in studies of children exposed to external radiation (Ron et al., 1995). For a dose of 1 Gy, the estimated relative risk of thyroid cancer varied from 5.5 (95% CI 3.1–9.5) to 8.4 (95% 4.1–17.3) depending on the risk model used. The models that best described the observed increase in risk were: the linear ERR model up to 1 Gy and up to 2 Gy and the linear-quadratic ERR model over the entire dose range (Figure 1). However, the latter model tends to underestimate risks up to 2 Gy. The OR at 1 Gy observed for total thyroid dose, as well as dose from ^{131}I alone and in combination with short-lived isotopes of iodine and tellurium was very similar, indicating that the risk is mainly related to ^{131}I exposure. Adjusting for doses from longer-lived radionuclides and external radiation had little effect on this risk estimate.

There was no evidence of a difference in risk between males and females (OR at 1 Gy: 5.3 (95% CI 2.8–10.1) in girls and 5.7 (95% CI -2.8–11.8) in boys) or by country (OR at 1 Gy: 5.1 (95% CI 2.9–8.9) in Belarus and 31.5 (95% CI 1.3–761) in the Russian Federation). Analyses of the effects of iodine deficiency and supplementation are discussed below. Analyses of the effects of other modifying factors (including age at exposure, reproductive factors (in girls and women), dietary factors, history of benign thyroid disease and family history of thyroid disease) are in progress.

An ongoing cohort study is being conducted by Belarusian, Ukrainian and U.S. scientists. The study cohort includes 25,161 subjects under the age of 18 years in 1986, who are being screened for thyroid diseases every two years. Individual thyroid doses are being estimated for all study subjects based on measurement of the radioactivity of the thyroid gland made in 1986 together with a radioecological model and interview data. More than one hundred histologically confirmed thyroid cancers were detected as a consequence of the first round of screening. The data will enable fitting appropriate dose-response models. Plans are to continue to follow-up the cohort for at least three screening cycles, which will lead to more precise estimates of risk. The first results are expected to be published soon (Stezhko et al., 2004)

The International Consortium for Research on the Health Effects of Radiation has conducted two population-based case-control studies of thyroid cancer in the Bryansk Oblast of the Russian Federation. The first focused on children and adolescents aged 0–19 years at the time of the accident, residing in the more highly contaminated areas (raions) of the Bryansk Oblast. Cases were diagnosed with thyroid cancer before October 1, 1997 *(n=26)*; two controls per case were identified from the Russian State Medical Dosimetry Registry and were matched by gender, birth year, raion of residence on April 26, 1986, and the type of settlement (urban, town, rural) *(n=52)*. Individual radiation doses to the thyroid were estimated utilizing a semi-empirical model and data collected in interviews, primarily of the participants' mothers. Based on a log-linear dose-response model treating estimated dose as a continuous variable, the trend of increasing risk with increasing dose was statistically significant. A manuscript describing these results was recently published (Davis et al., 2004)**.** Risk estimates from that study are similar to those seen in the larger case-control study of thyroid cancer in Belarus and Russia (Cardis et al., 2005). The second study extended case identification to include the entire oblast, and the period of diagnosis through August 1998. The results of the larger study, based on 66 cases of thyroid cancer and 132 controls, were similar to the results of the first study, revealing a significant dose response with increasing radiation dose from Chernobyl.

As indicated above, workers involved in Chernobyl clean-up activities were exposed to radiation. Although the dose to most of the clean-up workers was mainly from external gamma radiation, some of those who worked in the first days and weeks after the Chernobyl accident may have received substantial doses to the thyroid from iodine isotopes. Cohorts of clean-up workers from Estonia and Russia have been evaluated, and no association between radiation exposure and thyroid cancer was observed (Inskip et al., 1997; Ivanov, 2002). The studies of these workers, however, represent a relatively small number of the total clean-up workers, and there has been a suggestion of a possible risk among the very early workers (Ivanov, 1997), but this requires further substantiation.

A nested case-control study of thyroid cancer has been carried out among Chernobyl liquidators of Belarus, Russia, and the Baltic countries, coordinated by the International Agency for Research on Cancer (IARC) (Kesminiene et al., 2002). The study population consists of approximately 10,000 Baltic countries liquidators, 40,000 Belarus liquidators and 51,000 liquidators from five large regions of Russia), who worked in the 30 km zone in the period 26 April 1986 to 31 December 1987, and who were included in the Chernobyl registry of these countries. Overall, 115 cases of thyroid cancer and their respective controls have been interviewed. A method of analytical dose reconstruction (and estimation of associated uncertainties) using information collected by questionnaire together with dosimetry and environmental measurement data has been developed (RADRUE), validated extensively and applied to the estimation of doses and related uncertainties for all the subjects in the study. Dose reconstruction is completed, as well as estimation of dosimetry uncertainties and analyses are in progress.

Expert assessment (epidemiology)

Consensus

Existence of a causal relationship. In essence, there remains no doubt as to the existence of a causal relationship between exposure to radioactive iodines from the Chernobyl accident and increased risk of thyroid cancer seen in those exposed as children or adolescents.

Dose response. The magnitude of the dose response, i.e., of the excess risk for individuals as a function of dose to the thyroid, is not well established due to the limited number of published analytical studies, especially with individual dose estimates and adjustment for dose uncertainties. The magnitude of the risk appears to be slightly lower but similar to that seen following exposure in childhood to external radiation.

Modifying effects of age, time, gender and age at exposure. From the studies of atomic-bomb survivors in Hiroshima and Nagasaki and other studies of external irradiation, exposure at the youngest ages conferred the greatest risk of thyroid cancer (Ron et al., 1995; Thompson et al., 1994). The available data from an ecological study of the effects of radioiodine exposure from the Chernobyl accident in areas with relatively good dosimetry are largely in agreement with this observation (Jacob et al., 1999). A recent descriptive study has confirmed the age trend, finding the highest incidence among those exposed at ages 0–4, who also had the highest doses (Tronko et al., 2002). In future follow-up studies, the highest risk subgroup will be expressing thyroid cancer during young adulthood, and consequently this age group should be studied preferentially in the next few years.

The pooled analysis of cohorts exposed to external radiation during childhood or adolescence showed that thyroid cancer risk was still increased at the longest period of observation, about 45 years (Ron et al., 1995). The greatest relative risk was observed at about 15-30 years, and there was uncertainty as to whether there was a lesser risk or the same level of risk after that time. More than fifteen years after the Chernobyl accident, thyroid cancer incidence is still highly elevated (Tronko et al., 2002; Kenigsberg et al., 2002). Although longer-term, i.e. life-long, follow-up results at this time are not available under the circumstances of the Chernobyl accident, the best evidence derived from the external exposure studies would indicate that relative risk increases of thyroid cancer will continue for at least another decade at the current rate, after which it may decrease, but this remains uncertain (Ron et al., 1995).

A radiation-related increase in thyroid cancer is observed in both males and females. Some of the Chernobyl studies have reported similar relative risks per unit dose for males and females (Jacob et al., 1999; Cardis et al., 2005; Davis et al., 2004); another found a higher relative risk for males than females (Jacob et al., 1999). Since the background rates of thyroid cancer are several times higher in females than in males, this implies that more radiation-induced thyroid cancers occur in females.

Modifying effects of iodine status. Experimental studies indicate that iodine deficiency may be an important modifier of the risk of radiation-induced thyroid cancer (Thomas, Williams, and Williams, 1991; Kanno et al., 1992; Ohshima and Ward, 1986). Iodine deficiency affects not only the level of dose received by the thyroid gland at the moment of exposure but also, if continued, thyroid function in the years after exposure (Baverstock and Cardis, 1996; Gembicki et al., 1997; Yamashita and Shibata, 1997).

Although information from population surveys of thyroid volume, thyroid diseases and urinary iodine levels are available both before and after the accident, the information is far from comprehensive or consistent and cannot be used currently for the evaluation of the iodine status of individual study subjects in epidemiological studies. Environmental iodine measurements may be the most stable and informative indices for populations living in rural areas (whose diet is largely based on locally grown and produced foods). Investigations of diet in rural areas of the former USSR showed that vegetables and meat/milk provide most of the total iodine daily consumption (approximately 58% and 33%), while iodine in air and water account for about 4% (Vinogradov, 1946). Classification of iodine content in soils based on the soil type was frequently used in the former USSR in 60-70's to prepare maps of availability of stable iodine, in particular in Belarus (Lozovsky, 1971) and Kaluga region of Russia (Tiuriukanov, 1964).

A formal analytical study of the interaction between radiation dose and iodine deficiency on the risk of thyroid cancer was carried out in the most contaminated areas of Belarus and Russia (Cardis et al., 2005), within the joint Belarus-Russia-IARC-SMHF case-control study. For each subject in the study, the level of stable iodine in soil in the settlement of residence at the time of the Chernobyl accident was used as a surrogate of stable iodine status. This was derived from the estimated average iodine content in the predominant soil types in the land used for agriculture in the area around the settlements, based on a relation between soil type and iodine level (Lozovsky, 1971). A significant interaction was found between dose and iodine level in soil to the risk of thyroid cancer. The OR at 1 Gy in subjects living in settlements with the lowest soil iodine levels was 3.2 times higher (95% CI 1.9–5.5) than for those living in areas of greater soil iodine content.

Another study (Shakhtarin et al., 2003) in the Bryansk region has also investigated the relationship between iodine-deficiency, radiation doses and risk of thyroid cancer in young people. A joint effect of radiation dose and iodine deficiency was found: the ERR in territories with severe iodine deficiency was approximately twice that in areas with normal iodine intake. This suggests that iodine deficiency may enhance the risk of thyroid cancer following radiation exposure. Although the evidence is not conclusive, as the study is ecological and uses approximations for both radiation dose and iodine deficiency, the results are consistent with those of the case-control study described above.

The effect of stable iodine consumption in the years following the accident was also examined in the joint Belarus-Russia-IARC-SMHF case-control study (Cardis et al., 2005). Consumption of stable iodine following radioactive iodine exposure appeared to significantly reduce the risk of radiation induced thyroid cancer: the OR at 1 Gy in subjects who consumed antistrumin - a preparation containing potassium iodide used in the former USSR for goiter prophylaxis - was 0.34 times that of those who did not (95% CI 0.1–0.9). There was no statistically significant difference in the effects of antistrumin intake in areas of high and low soil iodine contents: consumption of antistrumin reduced the OR at 1 Gy from 3.5 to 1.1 in areas of higher iodine soil content, and from 10.8 to 3.3 in areas of low iodine soil content.

Estimating risk from ecological studies. The degree to which ecological studies can provide quantitative estimates of risk for thyroid cancer after the Chernobyl accident has not been fully explored to date. In other circumstances, the potential of ecological studies to provide quantitative risk estimates is known to be low. However, the strength of the radiation effect compared to confounding factors like screening after the Chernobyl accident and the large number of ^{131}I measurements in the thyroid are unique features of the Chernobyl circumstances, which may enable ecological studies to provide estimates of risk that are more useful than is typical of ecological studies. Moreover it may be possible to account for effects of geographical differences in screening intensity to further improve risk estimates from ecological studies.

Dose uncertainties. The quantitative effects of dose uncertainties on risk estimates are currently not known. Several ongoing, well designed cohort and case-control studies are attempting to evaluate uncertainties in individual dose estimates and to account for them in the estimation of risk.

Early detection screening, case detection and reporting. Large-scale screening programmes were initiated in contaminated areas shortly after the accident (UNSCEAR, 2000). Screening programmes, in general, increase the apparent incidence of thyroid cancer by advancing the time of diagnosis of tumours that would otherwise become clinically apparent only at some later date, and possibly by identifying tumours that would never become clinically manifest (Schneider et al., 1993; Thompson et al., 1994; Yoshimoto et al., 1995).

Since the Chernobyl accident, other related events have resulted in enhanced diagnosis and ascertainment of thyroid cancer in Ukraine, Belarus, and Russia. New, technically superior diagnostic tools have been introduced, with a particularly dramatic escalation in incidence observed shortly after the use of thyroid ultrasound began. Another aspect of the rise in thyroid cancer incidence is related to the heightened awareness of the relationship between Chernobyl and thyroid cancer. This awareness leads to more frequent and careful neck examinations at the time of either a routine medical visit or a visit for some other medical indication. Finally, heightened awareness leads to better and more complete disease reporting. The phenomenon of a screening-ascertainment-related increase in thyroid cancer has been observed in children in some oblasts that had minimal radiation contamination

(Likhtarev et al., 1995). Thus, the results of screening largely depend on the population studied and the screening protocol, especially the diagnostic tools employed and the frequency of screening.

Screening programmes have both potential benefits and risks, and the efficacy of a screening programme will vary depending on the level of risk of the screened population. Since screening with ultrasound usually detects a large number of clinically insignificant nodules, risk benefit analyses should be undertaken before initiating new programmes (Eden, Mahon, and Helfand, 2001).

Gaps in knowledge

Existence of a causal relationship. There is still considerable uncertainty as to the potential existence of a causal relationship in those exposed as adults. Although there have been some reported increases in those exposed as adults, this has not been related to dose and might be accounted for by the increased screening of the population.

The other gap in knowledge (as discussed below) relates primarily to the magnitude of the effect in those exposed as young people and the possible modifying effects of other environmental, genetic and host factors. Since the first WHO Expert Group Meeting (December 2003), new data from case-control studies have become available (Cardis et al., 2005; Davis et al., 2004). They provide more information about the magnitude of the risks associated with exposure to iodine isotopes. These appear to be slightly lower, but of similar magnitude to the risk seen following exposure in childhood to external radiation. One of these studies indicates, moreover, that iodine deficiency and subsequent dietary supplementation with stable iodine may both substantially modify the risk of radiation-induced thyroid cancer in young people.

In those exposed as adults, if a causal association is demonstrated, there will also be a need for more studies to quantify that association and examine any modifying effects by the above factors.

Dose response. Results from published studies of thyroid cancer in Chernobyl-exposed populations are qualitatively consistent, regardless of study design and the manner in which doses or exposures are characterized (UNSCEAR, 2000). Results of ecological studies for areas with relatively good dosimetry (Jacob et al., 1999; 2000) agree within the uncertainty bounds with risk per unit dose as they were observed after external exposures (Ron et al., 1995). Risk estimates based on analytical studies with comparable case ascertainment and individualized dose estimates and assessment of dose uncertainties are now available and indicate that the risk per Gy may be slightly less, but similar to (and statistically compatible with) that seen following external exposures.

The shape of the dose response for thyroid cancer has been evaluated, so far, only in one large-scale analytical study of thyroid cancer in young people (Cardis et al., 2005) and needs to be confirmed. Factors influencing this dose response also need to be confirmed, since very large numbers of persons were exposed to low doses. The optimal statistical methods for estimating and testing the statistical significance of dose responses in the presence of complex dose uncertainties have not yet been established. However this is an area of active methodological research that promises to provide important new statistical tools for analyzing radiation dose responses (Pierce, Stram, and Vaeth, 1990; Schafer et al., 2001; Stram, 2003; Thomas, Stram, and Dwyer, 1993).

Modifying effects of age, time, gender and age at exposure. There are differences between Ukraine and Belarus in the dependencies of the thyroid cancer incidence on age at exposure and on age at observation (Jacob et al., 2000). Differences in case detection and reporting may contribute to these discrepancies, however, the reasons are not yet fully understood.

A study of thyroid cancers diagnosed in adolescents and adults in the Bryansk region reported a small excess of thyroid cancer among adults (Ivanov et al., 2003a). The excess was not correlated with the imputed doses, but larger studies with longer follow-up and greater statistical power are needed. Other data on the risk of thyroid cancer from adult irradiation are being developed but have not yet been published. Of particular interest will be breakdowns within the adult age range, to determine if there may be increased risk following exposure at younger adult ages, as has been suggested by the Japanese atomic-bomb data (Ron et al., 1995; Thompson et al., 1994). One difficulty in interpreting the adult-exposure data is sorting out the effects of irradiation from those of increased surveillance for thyroid cancer or other causal factors. Ongoing case-control studies may provide more information on a variety of possible causal factors.

Another gap pertains to the risk of thyroid disease following *in utero* exposure to ^{131}I. The thyroid gland begins to become functional at about the 12th week of pregnancy and, given that immature tissues are often at high carcinogenic risk, may be highly susceptible to thyroid cancer induction by ^{131}I exposure. No data are currently available from Chernobyl regarding risk from *in utero* exposure.

In an ecological study in the area of Belarus with relatively good dosimetry (Jacob et al., 1999), the excess absolute risk increased from the period 1991-1993 to the period 1994-1996 by 25%. Although thyroid cancer risk is continuing at a high level, and there is no reason to expect a decrease in the next 15 or more years, at the present time the follow-up of Chernobyl-exposed children is too short to determine long-term risks.

Furthermore, there is considerable uncertainty as to how to project lifetime risks of thyroid cancer from Chernobyl. None of the current studies of external radiation have had more than about 45 years of follow-up, and the analysis of the pooled data could not resolve whether a constant relative risk model or a risk that peaked and then diminished at longer follow-up times (or older ages) was more appropriate. However, the difference in lifetime risk projections from those two models is probably not more than 2- to 3-fold (Shore and Xue, 1999). A constant excess absolute risk (EAR) model, however, did not adequately describe the risk in these populations.

The cohorts exposed to Chernobyl fallout during childhood and adolescence are now entering their reproductive years. Future studies should consider reproductive factors as possible modifiers of radiation risk, since some reproductive and hormonal co-factors appear to be weakly associated with spontaneous thyroid cancer risk (La Vecchia et al., 1999; Negri et al., 1999). Analyses of these effects are underway in the joint Belarus-Russia-IARC-SMHF case-controls study.

Modifying effects of iodine status. Only two studies to date (Cardis et al., 2005; Shakhtarin et al., 2003) have formally addressed the issue of an interaction between radiation dose and iodine deficiency on thyroid cancer risk. Further studies are needed to confirm the observed results.

Attempts have been made to establish the iodine deficiency levels in the areas of Belarus, Russia and Ukraine contaminated by the Chernobyl accident (Yamashita and Shibata, 1997; Ashikawa et al., 1997; Baverstock and Cardis, 1996), but these studies mainly address contemporary levels of iodine deficiency.

Prophylaxis from large amounts of stable iodine distributed to the population living near Chernobyl at the time of the accident may reduce the risk of thyroid cancer. However, stable iodine administration begun several days after ^{131}I exposure, rather than immediately, may instead enhance risk by slowing down the excretion of radioactive iodine (Reiners, 1994).

Only one study to date (Cardis et al., 2005) is available on the role of stable iodine prophylaxis on the risk of thyroid disease following radioactive iodine exposure. However, several studies now being conducted will have information on this, albeit determined by self/parental recall. Results need to be confirmed.

Estimating risk from ecological studies. The two primary gaps in knowledge when using ecological data to estimate risk measures are the absence of data on potential confounders such as the degree of screening in geographical areas, and secondly, the quantitative impact of the effect of confounders at the group level as well as confounders at the individual level, which cannot be taken into account in such ecological estimates. With further knowledge in these areas, the technique should provide a useful supplement to risk estimates based on analytical epidemiologic studies.

Dose uncertainties. There are two basic gaps in knowledge. The first is a lack of information on the nature, magnitude and type of uncertainty in dose estimation procedures, and the second lies in the development of appropriate statistical methods for taking such errors into account when making risk estimates. Data presently exist in both areas, but more sophisticated approaches to these two problems should serve to further clarify the impact of dose uncertainties on risk estimates. This investigation is in progress in a number of ongoing analytical studies.

Early detection screening, case detection and reporting. Both public health issues and interpretation of epidemiological studies need to be considered in regard to screening. With respect to public health, the first priority is to establish whether or not screening produces a net benefit in terms of mortality and/or morbidity, including quality of life. The potential risks to the patient, as well as the consequences for the medical care system, e.g. overload in terms of both personnel and equipment, need to be identified and appropriate cost- and risk-benefit analyses should be undertaken. Cost- and risk-benefit analysis should include not only morbidity and mortality associated with surgery, but also the need for long-term patient compliance and the necessity for life-long medication and follow-up.

In certain situations, screening has the potential to cause bias in epidemiological studies and the risk estimates derived from these studies (UNSCEAR, 2000). For example, if people with high radiation doses are screened more frequently or intensely than individuals with lower exposure, then a false positive association between dose and thyroid disease will probably be found. In particular, the absolute rate of thyroid cancer will be increased in a screened population. This means that the excess absolute risk estimate will be overstated and may not be generalizable to a non-screened population. The excess relative risk estimate would also be biased upward, if there is a correlation between thyroid dose and frequency of screening; however, if the screening was across the board for all dose groups, including the baseline group, then the excess relative risk estimate would be little affected by screening. The sparse available data generally support the notion that, once age at diagnosis is controlled for, relative risk estimates are less perturbed by screening bias than absolute risk estimates, and that the size, symptoms and aggressiveness of radiogenic and sporadic thyroid cancers are similar.

Adequate information on the potential degree of confounding by screening intensity is not currently available. As 40-70% of thyroid cancer cases (UNSCEAR, 2000) are detected by screening or are due to improved case detection and reporting, the degree of potential confounding on risk estimates from epidemiological studies needs to be evaluated carefully.

Conclusions (epidemiology)

A great deal has already been learned about the consequences of the Chernobyl accident for thyroid cancer. There is an increased risk of thyroid cancer, especially in those exposed at young ages. The greatest risks of radiation-related thyroid cancer have been observed in those who were children or adolescents at the time of the accident and those with the highest levels of exposure to radioiodine. However, much remains to be learned, including a precise characterization of the thyroid cancer dose response that accounts for the uncertainties in dose estimation and the effects of screening for thyroid disease, an understanding of the mechanisms of radiation carcinogenesis in the thyroid gland and how those mechanisms determine the dose response, and an understanding of the role of genetic predisposition and its effect on the thyroid cancer dose response.

The Chernobyl experience provides the best opportunity to learn about the effects of exposure to low doses from ^{131}I on thyroid cancer risk. While it may not definitively settle the question of the shape of the thyroid cancer dose response at low doses and dose rates, careful epidemiological and dosimetry study should provide important evidence for radiation protection measures.

There have been no published studies to date of the effects of exposure *in utero* and only very limited information on the effects of exposures during adulthood.

It is important to consider the strengths and limitations of each study in interpreting results regarding the risk of thyroid cancer after Chernobyl. Results of analytical studies (e.g., case-control and cohort studies) now becoming available provide more informative quantitative estimates of risk of thyroid cancer after the Chernobyl accident than earlier ecological studies.

Based on studies of other populations exposed to external radiation that have had long follow-up times, it is expected that thyroid cancer risk from Chernobyl will continue for many more years, although the long-term magnitude of risk is difficult to quantify.

New studies indicate that iodine deficiency and supplementation may play a role in radiation-related thyroid cancer after Chernobyl. Further studies are needed to replicate these findings, but the role of iodine deficiency and iodine supplementation on this risk have not been adequately studied.

Screening and case detection and reporting have important implications in the areas of public health and thyroid cancer risk estimation, yet we lack quantitative data regarding their effects in either of these areas.

Recommendations (epidemiology)

Continued monitoring of persons exposed as children is a public health priority for the foreseeable future.

For health planning purposes, continuous estimation of the predicted number of cases of thyroid cancer expected to occur in exposed populations should be based on updated estimates of risk in those populations.

Investigations of the risk of thyroid cancer as a result of the Chernobyl accident should be based on analyses of radiation dose response, utilizing individualized dose estimates whenever possible. The uncertainties of these dose estimates should be carefully analysed and accounted for in the estimation of dose responses.

It is recommended that there be an increased focus on the use of analytical study designs because of their suitability for deriving quantitative estimates of disease risk for individuals and for exploring modifying effects. Ecological studies, however, also should be continued, especially since they are helpful in determining how best to allocate scarce public health resources, documenting geographical and temporal variation in risk, and providing approximate risk estimates based on large numbers of cases.

The development of techniques and standards for statistical analysis of radiation dose response with complex dose uncertainties is an area of active research, and analyses of the thyroid cancer dose response should capitalize on these developments. Analyzes of thyroid cancer dose responses should also take into account all available information regarding 1) methods of case detection and reporting (to account for possible biases arising from differences in case ascertainment that may be correlated with dose), and 2) potential confounding factors or dose effect modifiers such as age at exposure, age at risk, gender, stable iodine sufficiency/deficiency, and stable iodine prophylaxis around the time of the accident.

Epidemiological surveillance and research in the regions currently being studied should continue. Further study will permit more sophisticated and accurate modeling of risk, perhaps with models that are less empirical, and more firmly rooted in biological mechanisms, than those currently used. It is particularly important that further surveillance and research emphasize those who were children or adolescents at the time of the Chernobyl accident, although more assessment of risk among those who were adults (especially young adults) is also needed.

High quality cancer registries should continue to be supported. They will be useful not only for epidemiological studies, but also for public health purposes, e.g., providing reliable information to help guide the allocation of public health resources.

Results of multiple studies of thyroid cancer risk should be examined critically in order to understand any differences in results and to determine how combined risk estimates can be derived. These multiple studies may be of different designs and rely on different types of dose estimates.

Presently, it is not possible to exclude an excess risk of thyroid cancer in persons exposed to Chernobyl radiation as adults. Carefully designed and appropriately analysed studies should be conducted to provide more information on ^{131}I related risks following adult exposure.

Persons exposed to ^{131}I *in utero* should be studied, as there is no information on thyroid cancer risk in this potentially susceptible subgroup.

The impact of iodine deficiency (both at the time of the accident and in the years following) on the risk of radiation-induced thyroid cancer appear to be an important modifier of thyroid cancer risk. This should be confirmed in further studies using adequate and validated historical estimates of iodine status.

Within existing screening programmes for exposed individuals, cost- and risk-benefit analyses to assess the net value of screening should be conducted. The results of these analyses should also be used to tailor screening programmes to specific populations based on risk profiles (e.g. those who were children or adolescents at the time of the accident, those likely to have received high doses). If new screening tools become available, their efficacy should be investigated in a cost- and risk-benefit context before they are incorporated into a large-scale screening programme.

More detail is needed on the degree of screening and of improved case detection and reporting as a function of time and geographic area, so that this information can be taken into account in the analysis of epidemiological studies. With regard to analytical epidemiological studies (case-control or cohort), it will be important to identify screening and surveillance-related behaviour for both cases and controls (non-cases for cohort studies) and to take such information into account in the analysis.

Biological Aspects

Pathology

Current status of studies

Thyroid cancers derived from the follicular cell can be divided into two main types, papillary and follicular cancers. Papillary cancer arises de novo from the follicular epithelial cell. Follicular cancers are morphologically similar to follicular adenomas, which are benign lesions. Evidence of invasion through the capsule, into veins or extrathyroid tissues distinguishes carcinoma from adenoma. Papillary and follicular cancers show different clinical and molecular biological features as well as characteristic morphological features. Diagnosis is made on a number of features that are characteristic of papillary cancers (there are characteristic nuclear features - grooved pale nuclei, that frequently show intranuclear cytoplasmic inclusions, and the tumours contain calcified structures called *psammoma* bodies); these features are lacking in follicular tumours. The diagnosis of papillary cancer depends on the presence of a number of these features, but all do not have to be present for a diagnosis of papillary cancer to be made.

In addition to the two main types of cancer derived from the follicular cells, there are a number of subtypes of papillary cancer. These are named on the dominant structural component. The classic papillary cancer, most commonly found in adults, is composed of papillary structures; the follicular variant of papillary cancer is composed of follicular structures but has the nuclear features and *psammoma* bodies that are indicative of papillary cancer; and the solid or solid-follicular variant is composed of solid sheets of cells with or without a follicular component. The latter variant shows variable nuclear features, but does contain *psammoma* bodies.

The majority of thyroid cancers diagnosed in those who were children or adolescents at the time of the accident in Belarus and Ukraine are papillary cancers. This is the most common of the two main types of thyroid cancer in unexposed populations. Early reports of the pathology of post Chernobyl thyroid cancer suggested that there was a particularly high frequency of the solid and solid-follicular variants of papillary cancer. These subtypes of papillary cancer are also seen in young children who were not exposed to radiation. An international panel of expert thyroid pathologists has reviewed all cases (aged under 19 at the accident) of thyroid cancer that have occurred in the contaminated areas of Ukraine and Russia from October 1998 to date that are included in the Chernobyl Tissue Bank (see below), and all those that have occurred in Belarus from October 1998 to February 2001. While in the majority of cases it has been easy to distinguish papillary cancers from follicular cancers, there are a few cases where a definitive diagnosis has not been possible. This type of intermediate lesion is also seen in non-radiation exposed populations and has led to a suggested reclassification of thyroid tumours (Williams, 2000)

The UNSCEAR 2000 report suggested on the evidence then available that there may be a link between the morphological subtype (i.e., solid-follicular variant) of papillary cancer observed in children exposed to radiation. More recent evidence raises questions as to this causal relationship between solid-follicular morphology of papillary cancer and radiation exposure. The morphology and aggressiveness of papillary cancers groups was shown to be a function of latency in groups of children exposed at different ages, and was suggested to be independent of age at exposure (Williams et al., 2004). The proportion of papillary cancers that are composed mainly of papillae increases with time post accident, while the solid-follicular variant appears to be decreasing with time post accident (Tronko et al., 2002; 2003). This is illustrated with data from Ukraine below (Figure 2). In addition, the percentage of small papillary cancers (less than or equal to 1 cm) appears to be increasing with time (Tronko et al., 2002; 2003). This could be a function of more sensitive screening or a decrease in growth rate or aggressiveness.

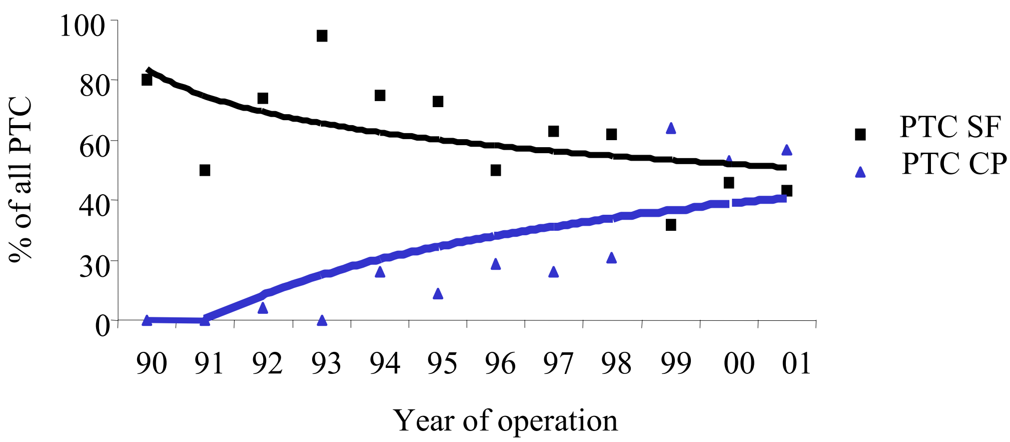

Figure 2: Change with time in the proportion of papillary carcinoma subtypes with time post accident. PTC CP = subtype composed mainly of papillae, PTC SF = solid-follicular subtype.

Molecular biology

Current status of studies

Earlier studies reported that there was a higher than expected frequency of ret rearrangement in post Chernobyl thyroid cancer, suggesting some ret rearrangements might be regarded as a marker for radiation exposure (Klugbauer et al., 1995; Fuggazzola et al., 1995). Other papers have suggested that there is not a link between radiation exposure and ret rearrangement. However, there have been few statistically valid studies of ret rearrangement in non-Chernobyl associated pediatric thyroid cancers (Williams et al., 1996, Fenton et al., 2000), making substantiation of the association of ret rearrangements with radiation exposure difficult. It is important to remember that the correlation between molecular biology and pathology is not absolute: in all of the series published so far, a substantial proportion (30-50%) of the papillary cancers do not harbour a ret rearrangement. A variety of different techniques have been used to assess the frequency of ret rearrangement and, although this may explain the variation in frequency of ret rearrangement among studies, there still remains a large proportion of papillary carcinomas for which alternative molecular pathways need to be identified. Moreover a few studies have demonstrated ret rearrangements in benign tumours associated with radiation exposure (Elisei et al., 2001; Bounacer et al., 1997) however, other studies have failed to substantiate these findings (Thomas et al., 1999), adding further uncertainty to the specific association of ret rearrangement with papillary thyroid cancer.

Despite the evidence that *ret* is able to transform the follicular cell *in vitro*, the evidence from the transgenic mice suggests that other oncogenic mutations must be required for development of the tumour. The clinical relevance of *ret* rearrangement in post Chernobyl papillary carcinoma still remains unclear. Some studies in adults have suggested that the presence of ret rearrangement may confer a better prognosis, but other studies suggest the opposite (Sugg et al., 1996; Bongarzone et al., 1998; Musholt et al., 2000; Basolo et al., 2001). In addition, it has also been suggested that ret rearrangements are not found in all cells in post Chernobyl papillary carcinomas, and that cells harbouring the rearrangement may be clustered. This suggests either a polyclonal origin for these tumours, or that *ret* rearrangement is a later event in thyroid papillary carcinogenesis than had previously been thought (Unger et al., 2004).

In addition, the B-*raf* oncogene has recently emerged as the most commonly mutated oncogene in papillary carcinoma in adults. The frequency varies in a number of studies from 36-69% in adult PTC (Cohen et al., 2003; Kimura et al., 2003; Soares et al., 2003), including one study on Ukrainian tumours (Powell, Jr. et al., 1998; Powell et al., 2005). The frequency of B-*raf* mutation in post Chernobyl cases (aged under 18 at operation) is much lower, of the order of 7% and does not appear to be significantly different from that observed in sporadic childhood thyroid papillary carcinoma (Nikiforova et al., 2004; Lima et al., 2003). This finding is perhaps not surprising, as B-*raf* and ret oncogenic alterations appear to be mutually exclusive in the series published thus far. However, it is clear that all cases that are negative for B-*raf* in young onset papillary cancer are not necessarily positive for ret rearrangement, and that there are as yet unidentified oncogenic changes in these tumours.

To further complicate matters, there is now evidence that the morphology of post Chernobyl papillary cancer is changing with time post accident (Williams et al., 2004; Tronko et al., 2002). This suggests that the molecular profile observed in the early cases may owe more to the age of the patient at diagnosis rather than the etiological agent. Although the rate of the rise of papillary carcinomas appears to be slowing in those aged under 19 at operation, it may be that as with other types of radiation induced cancers, such as leukaemia, there are a number of different subtypes of the disease that show different latencies. This may be further complicated by differential effects of radiation depending on the age at exposure of the patient.

The evidence so far suggests that the molecular biology of post Chernobyl childhood thyroid cancer is similar to that seen in age-matched series from non irradiated populations. Post Chernobyl papillary thyroid carcinomas, in common with non-radiation associated childhood papillary carcinomas do not harbour *ras* mutations (Santoro et al., 2000), or p53 mutations (Suchy et al., 1998), or show micro-satellite instability (Santoro et al., 2000). They do show a higher frequency of ret rearrangement and a lower frequency of B-*raf* mutation than papillary carcinomas diagnosed in adulthood. Whether these oncogenic changes are related to the pathology of these tumours, or their latency, rather than their etiology remains to be understood.

Studies have also been carried out into the expression of other receptor tyrosine kinases in post Chernobyl thyroid cancers, e.g. axel and its ligand Gas6 (Ito et al., 2002) and the involvement of mutation in the mitochondrial genome (Lohrer, Hieber, and Zitzelsberger, 2002, Rogounovitch et al., 2002; Lima et al., 2003). However, these studies are inconclusive with respect to relationship to radiation exposure, as they do not compare the frequency of these oncogenic rearrangements with appropriate age matched controls.

The majority of studies focus on assessing frequency of one or two oncogenes in a series of tumours. Studies using cDNA array enable the study of multiple changes in gene expression. One recent cDNA array study suggests that the overall profile of post Chernobyl papillary cancers are similar to papillary carcinomas from Belgium and France (Detours et al., 2005).

With the exception of the post Chernobyl group of patients, the majority of patients treated with radioiodine for thyroid cancer have been adults. Thus far no risk of secondary tumours has been identified. However, there is evidence in the literature that urges caution with therapeutic radiation exposure in childhood and adolescence. Experience with external radiation exposure to the chest in children with Hodgkin’s disease shows that some patients show an increased risk of lung and breast tumours among others (van Leeuwen et al., 2003; Bhatia et al., 2003). There will have been considerable exposure to the lungs, and possibly breast, from therapeutic ^{131}I in those children presenting with papillary cancer metastatic to the lungs. Evidence suggests that those who were treated in childhood with therapeutic radiation are most at risk from the later development of breast cancer (in females) and lung cancer (both sexes) (Swerdlow et al., 2000). Genetic susceptibility is one factor that is likely to play a role in the development of secondary tumours (or possibly pulmonary fibrosis) post therapy. The genes or polymorphisms that led to this susceptibility may be either common or different to those that we suspect would be identified in studies of susceptibility to development of primary thyroid cancer following exposure to iodine deficiency. Other factors (e.g. for breast cancer: age at first full term pregnancy, menstrual history; for lung cancer, smoking, and occupational exposure to other carcinogens) may also play a role in susceptibility to development of site-specific tumours. Studies of molecular biology in this area should be combined with lifestyle questionnaire data in order to address these questions. Investigation of secondary tumours following therapeutic radiation may provide insight into the genes/lifestyles that could alter the risk of development of secondary detrimental effects post radioiodine therapy for thyroid cancer early in life.

The research studies so far have concentrated on papillary carcinoma as this has been the most frequently observed type of thyroid tumour post Chernobyl. It remains to be established whether there is also an increase in tumours of the follicular series post Chernobyl. If so, the above studies should be carried out in follicular tumours in order to ascertain whether a radiation signature can be identified for this type of lesion.

Chernobyl Tissue Bank

Current status of studies

The Chernobyl Tissue Bank (www.chernobyltissuebank.com) was established to provide material for molecular biological research into post Chernobyl thyroid tumours (Thomas et al., 2000). This project integrates a number of research projects in different countries and provides a pooled dataset on the results of the various studies. The material held in the bank has been reviewed by an international panel of expert thyroid pathologists, and all extracted nucleic acid samples are subject to extensive quality control. Researchers are provided with a minimum dataset (date of birth, date of operation, place of residence at the time of the accident, sex, the consensus diagnosis from the pathology panel); further more detailed pathology and clinical information is held in the two Eastern European Institutes that participate in this project (the Institute of Endocrinology and Metabolism, Kiev and MRRC RAMS in Obninsk). The studies so far supported encompass research groups from Japan, the U.S. and 6 European countries, and include single and multi-gene, cDNA array and comparative genomic hybridisation (CGH) studies (Thomas and Williams, 2001). The results from each of the research projects using the resource are returned on a case-by-case basis and entered into a database for later correlation. Many of the studies quoted above have utilized material from the resource, and applications from other interested groups are welcome. Information on how to access material from the Chernobyl Tissue Bank can be obtained from the project website (www.chernobyltissuebank.com). The website also contains a bibliography, updated monthly, on published papers on Chernobyl and thyroid cancer.

Expert assessment (biological aspects)

Consensus

There is no doubt that the large rise in thyroid cancer observed in those who were young at the time of the Chernobyl accident and resident in the areas of Belarus, Ukraine and Russia closest to the reactor, is due to exposure to radioiodine in fallout. The rise is confined largely to one type of thyroid cancer - papillary cancer, which derives from the iodine concentrating follicular cells.

Gaps in knowledge

Studies that continue to monitor the pathology of post Chernobyl thyroid cancer now suggest that while papillary carcinoma remains the most frequently observed type of thyroid tumour in the population exposed while young, the morphology of the tumours is changing with time post accident. There will be a natural increase in spontaneous thyroid cancer as the exposed cohort ages, and this must be borne in mind in interpreting the data, but the findings of these initial studies may have important implication for studies on the molecular biology of post Chernobyl thyroid cancer. The morphology of a tumour must reflect the integration of the molecular biological changes that have occurred during the genesis of the tumour cell population, and the natural biology of the tumour must be influenced by the intracorporal environment in which the tumour develops. This latter aspect has not yet been considered adequately in cancer research for the thyroid or any other tissue.

Studies to determine whether the molecular biology of post Chernobyl thyroid cancer is different from the molecular biology of spontaneous thyroid cancer are hampered by the lack of availability of a large age-matched series of spontaneous thyroid cancers. Initially the unusually high levels of ret rearrangement observed in the first small studies reported led to the suggestion that ret rearrangement was a marker for radiation association; more recent studies suggest that this is not the case. However, due to the lack of information on a large series of papillary cancers in children aged under 10 at operation, it will be difficult to confirm or deny the relationship between particular rearrangements of the *ret* oncogene and radiation exposure.

A molecular signature for post Chernobyl thyroid cancer has yet to be established.

There may be differences in latency between different types of thyroid cancer. Although the rise in thyroid cancer thus far is due almost entirely to an increase in papillary carcinoma, there is evidence to suggest that there may be an increase in the other morphological type of tumours that derive from the iodine concentrating follicular cells, the follicular adenoma (benign) and carcinoma (malignant).

The relationship between this suspected increase in follicular tumours and radiation exposure must be established, and similar molecular biological and pathological studies should be carried out on these tumours.

The studies completed so far have concerned mainly the increase in thyroid cancer in those who were young at exposure. These studies suggest that there is a greater risk of development of thyroid cancer that is greater for the young at exposure. The studies have been facilitated by centralized treatment for thyroid cancer in the young - treatment of adults with thyroid cancer is more usually carried out at regional hospitals rather than one centralized clinic. There is uncertainty over the risk of exposure at older ages, although studies of iatrogenic exposure following the atomic bombings suggest that it is much lower. A recent paper (Franc et al., 2003) validated the diagnosis of thyroid cancer in the registries of Ukraine and Belarus. Further studies of the effect of radiation on those who were adult at the time of exposure may be therefore possible using registry data without histological review.

Conclusions (biological aspects)

Papillary cancer continues to be the primary pathological type of thyroid cancer in those exposed as children and adolescents to fallout from the Chernobyl accident. There are a variety of subtypes of papillary cancer, and it appears that these may be related to latency, and therefore are changing with time since exposure. It is not clear whether this change in morphology is related to clinical presentation or outcome.

At the molecular level, it would appear that the earlier suggestions that specific rearrangements of the ret oncogene may be a marker for radiation exposure have not been substantiated. Analysis of mutation in individual genes has not identified differences between radiation associated thyroid cancers, and age matched non-irradiation related cancers of similar morphology. However, it is clear that there are major differences in the molecular biology and pathology of papillary cancers as a function of age at clinical presentation. From initial studies on multiple gene expression analysis it is not clear that a radiation signature can be identified at this time.

The molecular biology and the pathomorphology of post Chernobyl thyroid cancer is dynamic, and a considerable effort needs to be maintained in monitoring both of these features with time post Chernobyl. Attention must be paid to the interpretation of the molecular biology studies, in particular the sensitivities of the different techniques used. Thyroid cancer is still the only cancer to show a proven rise in incidence post Chernobyl, but continued monitoring of other tumour types should be carried out to determine whether it will remain the only cancer to show an increase in this population.

Recommendations (biological aspects)

Further research is necessary to elucidate whether a molecular signature associated with radiation can be found in papillary cancer.

Studies using higher density cDNA microarrays and including more cases are needed before definitive conclusions can be drawn. From the clinical point of view, cDNA microarray analysis may permit separation of clinically more aggressive tumours from their less aggressive counterparts. Thyroid papillary cancers, even in these young persons, appear to have a relatively good prognosis. Gene expression analysis in terms of decisions relating to therapy has proved clinically valuable for other tumour types (van de Vijver et al., 2002). However, as thyroid cancer is effectively treated by radioiodine, and there are very limited options for chemotherapy, this approach may not prove a useful avenue.

In addition to investigations at the transcriptome level, investigations should also be made at the proteomic level, including all post translational modifications. A recent paper suggested that only 25-30% of changes observed at the transcriptome level correlated with changes in expression at the protein level.

The identification of serum markers that could be used for diagnosis or prognosis warrants further investigation in the cohort of patients exposed to radiation where long term follow up is strongly recommended.

In addition, studies on thyroid cancer should be carried out at the genetic level to determine whether there are allelic variations (e.g. single nucleotide polymorphisms or mutations) that may alter predisposition to the development of specifically radiation induced thyroid cancer or predispose to thyroid cancer in general. Animal models may be considered for determining genes of interest.

Further investigations should address the effect of latency on the pathology and molecular biology. Special care should be taken to collect material from children born after the accident and resident in the relevant areas of Ukraine, Belarus and Russia in order to permit future studies of thyroid tumour due to exposure to radioiodine versus the effect of low-level exposure to longer-lived isotopes such as ^{137}Cs; however it may prove to be difficult to separate the effect of exposure to low levels of radiation from the natural spontaneous incidence rate. Consideration should also be given to integrating collection of fresh material from sporadic cases from unexposed areas outside Belarus, Ukraine and Russia, so that modern molecular biological techniques can be performed on appropriate age-matched groups.

Similar efforts are needed with respect to tumours of the follicular series (adenomas and carcinomas), which some studies suggest may be arising with a greater latency than papillary carcinoma.

The majority of thyroid carcinomas respond to radioiodine therapy; a minority lose the ability to take up and concentrate radioiodine. Thyroid cancers do not respond well to conventional chemotherapy. The identification of the global regulatory networks in thyroid cancer cells will permit identification of targets for novel therapeutic agents (e.g. inhibitors of tyrosine kinases), which may be effective in treating thyroid cancers. This type of approach has proved useful in therapy of other types of tumour, e.g. the use of inhibitors of the abl/PDGFR tyrosine kinase (Buchdunger, O'Reilly, and Wood, 2002; Demetri et al., 2002), in specific types of leukaemia and gastric tumour, or the her2 receptor in breast cancer (Yarden, 2001).

Follow-up studies are needed of patients treated with radioiodine for metastatic deposits in the lungs, combined with studies of genetic polymorphism related to sensitivity to radiation carcinogenesis, both in relation to primary thyroid cancer as a result of exposure to fallout and in relation to development of secondary tumours following iatrogenic exposure.

Clinical Aspects

Oncology: updates on treatment, survival, recurrence, late effects

Post-2000 studies on the epidemiology of childhood thyroid cancer after Chernobyl are in line with earlier findings. Farahati et al. (2000) reported an inverse association between age at exposure and severity of the disease in children from Belarus with thyroid cancer. Compared with older children, the youngest group (2-4 years of age) showed more frequently extra-thyroidal invasion of tumour, more lymph node involvement and distant metastases.

Few publications are available on surgical and radiological treatment regimens of thyroid cancer in Chernobyl children, on complications of treatment, survival, and long-term follow-up of patients including quality of life. Total thyroidectomy and radioiodine treatment remain the treatment of choice (Reiners and Demidchik, 2003). Rybakov et al. (2000) reported results of combined (surgical and radioactive iodine) treatment of 330 children in the Institute of Endocrinology in Kiev. More than half of the patients were residents of the most contaminated areas. Their cancers developed after a shorter latency period, were more aggressive at manifestation, and expressed regional and distant metastases in 57% and 14.5% of cases, respectively. Papillary carcinoma was diagnosed in 93% of patients. To date, cancer recurrence was operated on 2.8%, and general mortality was 1.8%.

Between 1986 and 2002, 1152 consecutive childhood and adolescent patients were operated on in the Center for Thyroid Tumours in Minsk, Belarus (mean age 13.5 years) (Demidchik et al., 2005). The primary thyroid tumour was differentiated cancer in 99.3% and medullary cancer in 0.7%. Multifocality was noted in 190 (16.5%), and 767 (66.6%) had pathologically involved lymph nodes. Extraglandular extension was present in 159 (13.8%), and 23 (2.0)% had x-ray positive pulmonary metastases at presentation, while distant metastases were observed in 13.5% during later follow-up by ^{131}I scan, mostly in those who were not submitted to thyroidectomy. The majority of children underwent total thyroidectomy with simultaneous lateral neck dissections. Postoperative permanent hypoparathyroidism occurred in 9.3% of all patients, with the highest incidence in patients with total thyroidectomy and radical removal of bilateral lymph nodes. Permanent recurrent laryngeal nerve palsy occurred in 5.6% of patients. Patients with small cancers without evidence of metastatic disease were followed-up under suppressive therapy with levothyroxine, while the other patients received ablative radioiodine treatment. To date, local recurrences of carcinoma were diagnosed in 12.3%, mostly in those who were not submitted to radioablation.

Published data about post-operative ablation treatment with ^{131}I after near-total thyroidectomy in 249 young patients of the Ukraine are available (Oliynyk et al., 2001). However, only 52% of the patients were successfully ablated after 1-2 courses of radioiodine. The authors indicate that thyroid ablation in this particular category of patients with differentiated thyroid carcinomas is difficult to achieve due to the young age of the patients, and the use of relatively less radical surgery procedures on such patients.

A selected group of 220 children from Belarus with advanced stages of differentiated thyroid cancer, who presented with papillary thyroid cancer (99%) after the Chernobyl accident (with a mean latency of 7 years) has been treated by thyroidectomy in Minsk and consecutive radioiodine therapy in Essen and Würzburg, respectively (Reiners, 1998). The results can be summarized as follows: In 168 out of 202 children (83%), who received at least 2 courses of ^{131}I-treatment for ablation of remnants (50 MBq/kg of bodyweight), complete (i.e. negative whole-body scan and serum thyroglobulin undetectable) or stable partial remission could be observed (i.e. negative whole-body scan and thyroglobulin measurable but < 10ng/ml). In the subgroup of 100 children with lung metastases receiving between 2 and 8 courses of ^{131}I treatment (100 MBq/kg of bodyweight), the percentage of stable partial remissions amounted to 65%. The mean time required for complete or partial remission in children without out-distant metastases was 1.8 years, and in children with distant metastases 3.2 years. If strict criteria were applied setting the cut-off for thyroglobulin to 1 ng/ml, 35% of the total group and 28% of children with distant metastases are in complete remission. These results extend a previous report on a small group of children in Belarus, indicating that by adequate treatment the outcome is generally favourable and substantially similar to that of the naturally occurring papillary thyroid carcinoma (Ferdeghini et al., 1999). Since complete remission especially of lung metastases is difficult to achieve in children with differentiated thyroid cancer, the indication for repeated fractionated radioiodine therapy should be discussed critically, since the risk for radiation induced pulmonary fibrosis in this patient group has to be seriously taken into consideration (Reiners, 2003). In the analysis of 71 cases of pulmonary metastases in children, radiological signs of early manifestations of pulmonary fibrosis after ^{131}I therapy were found in as many as 17 children; although, clinically relevant pulmonary fibrosis was observed only in one case (Reiners and Demidchik, 2003; Reiners and Demidchik, in press). Because of the relatively high risk of development of pulmonary fibrosis after radioiodine therapy, research on modifying factors is needed.

The standard treatment for differentiated thyroid cancer, in addition to total thyroidectomy and ablative radioiodine therapy, also includes thyroid-stimulating hormone (TSH) suppressive therapy with levothyroxine (L-T_4). This is justified by the notion that most differentiated thyroid cancers express TSH receptors, and TSH promotes the growth of thyroid carcinomas (Mazzaferri and Kloos, 2001; Gemsenjager et al., 2000). Consequently, patients with thyroid carcinoma are usually treated with L-T_4. In adults, approximately 1.5 µg of L-T_4 has to be administered for suppression of TSH. In children, this dose depends on age, with the need for higher doses in smaller children, as demonstrated in studies on congenital hypothyroidism (Chiovato et al., 1991). Besides that, the efficacy of TSH-suppressive thyroid hormone therapy depends on the bioavailability of the L-T_4 preparation used. There may be considerable differences between preparations offered by different manufacturers. It is therefore necessary to control optimal TSH-suppression by monitoring the serum concentrations of TSH and free thyroid hormones). In addition, the quality of assay reagents from different manufacturers varies considerably. Therefore it is necessary to ensure sufficient supply of high quality L-T_4 and assay reagents in the countries affected by the Chernobyl accident. In this context, treatment of post-thyroidectomy hypoparathyroidism has to be mentioned specifically, since synthetic Vitamin D of adequate pharmacological quality (Calcitriol) is rarely available in the countries affected by the Chernobyl accident. With respect to surgical research, allogenic transplantation of encapsulated parathyroid tissue for replacement of hypoparathyroidism is an important issue.

Thyroid hormones when given in doses that lower TSH secretion to well below normal result in sub-clinical thyrotoxicosis (Mazzaferi, 2000). Longstanding sub-clinical thyrotoxicosis may have a number of adverse effects, notably on the bones and the heart (Wiersinga, 2001). Bone mineral density decreases in post-menopausal women treated with TSH-suppressive doses of L-T_4 (Uzzan et al., 1996). The question of whether this also occurs in men or pre-menopausal women has also been discussed (Marcocci et al., 1997). Bone loss was also observed in a single study of 20 children and adolescent females of a mean age 14.5, treated with high doses of L-T_4 for a mean period of 3 years (Radetti et al., 1993). The few available data in children raise some concern that TSH-suppressive doses of L-T_4 may influence growth development and reduce peak bone mass, which is reached in early adulthood (Von Harnack et al., 1972). Systematic longitudinal studies of calcium metabolism and bone mass and muscle-bone relationships in 208 Belarusian children after thyroidectomy because of thyroid carcinoma, however, did not reveal severe disturbances of skeletal development if calcium/vitamin D deficiency was corrected (Schneider et al., 2004).

Some sparse data indicate that sub-clinical thyrotoxicosis may also be associated with cardiovascular abnormalities, such as increased left ventricular mass, diastolic dysfunction, higher heart rate, more atrial extrasystoles, and an increased risk of atrial fibrillation (Sawin et al., 1994; Biondi et al., 1994; Fazio et al., 1995). Moreover, it has recently been reported that heart abnormalities associated with the impairment exercise performances occurring as a consequence of long term therapy with fixed TSH suppressive doses of L-T_4 may well be avoided by careful individual dose tailoring of TSH suppressive therapy (Mercuro et al., 2000). Other studies, however, indicate minimal cardiac effect in asymptomatic athyreotic patients chronically treated with TSH-suppressive doses on L-T_4 (Shapiro et al., 1997). The long-term effects of TSH-suppressive therapy in childhood thyroid cancer patients have not been fully investigated and deserve closer scientific attention.

Adjuvant external radiotherapy in adult patients with extra-thyroidal papillary thyroid carcinoma reduced in a non-randomized study the risk of distant metastases (Farahati et al., 1996). This observation has not been confirmed up to now. In children, adjuvant external radiotherapy does not appear to be indicated. In some patients with metastatic thyroid cancer treated with radioiodine, the uptake decreases with time due to de-differentiation of cancer cells. Retinoids have been shown in preliminary studies to promote re-differentiation in selected adult patients (Simon et al., 2002). This approach may be taken into consideration in selected adolescents with metastatic or recurrent de-differentiated thyroid cancer too. In patients under TSH-suppressive therapy, whole-body scanning requires withdrawal of L-T_4 for a relatively prolonged period of time, resulting in hypothyroidism. This condition is associated with unpleasant symptoms and could be critical in the developmental age. To prevent such side-effects of iatrogenic hypothyroidism, recombinant TSH (rhTSH) has been used in adults effectively (Haugen et al., 1999; Pacini and Lippi, 1999; Schlumberger, Ricard, and Pacini, 2000) and may be even more usefully applied in children and adolescents; however, up to now, no experiences with rhTSH are available in this patient group.

Side-effects of the ^{131}I treatment for thyroid cancer

Salivary and lacrimal gland tissues are both very radiosensitive and may be damaged as a secondary effect of ^{131}I therapy. After ^{131}I therapy a significant percentage of patients (20-30 %) may develop concurrent salivary and lacrimal gland dysfunction (sicca syndrome) in the following years. Although in the majority of cases these side effects develop early and are transient, they can persist for up to 3 years or appear later (Solans et al., 2001). No significant dependence on cumulative administered activity was found for objective xerostomia or xerophtalmia, but doses >11.1 GBq (300 mCi) were related to moderate-severe dysfunction on the salivary gland scintigraphy. There are neither prospective nor retrospective studies on salivary and lacrimal radiation induced dysfunction in childhood thyroid carcinoma.

Pulmonary fibrosis occurring in children and adolescents with lung metastases from papillary differentiated thyroid carcinoma submitted to radioiodine therapy has been documented in the past (Ceccarelli et al., 1988). In a series of 49 children with differentiated thyroid cancer and pulmonary metastases, 72% of subjects treated with radioiodine had radiological signs of early manifestation of pulmonary restrictive disease, from mild to severe, which persisted even when lung metastases were cured. However, only one patient died of respiratory failure due to diffuse lung metastases that had been treated with a total of 500 mCi of ^{131}I (Ceccarelli et al., 1988). The development of pulmonary fibrosis after radioiodine therapy has been observed by Reiners and Demidchik in 1 out of 71 Belarusian children with pulmonary metastases treated with radioiodine therapy, although radiological signs of pulmonary fibrosis were found in 17 out of 71 children (Demidchik and Reiners, 2003). Further prospective studies on children treated with high doses of ^{131}I for lung metastases are needed.

Transient increase in serum FSH level with or without azoospermia has been observed in about 1/3 of men treated with ^{131}I for differentiated thyroid carcinoma and is related to the cumulative dose of radioiodine administered. Permanent impairment of spermatogenesis may occur after multiple ^{131}I treatments (Pacini et al., 1994). A significant irradiation is delivered to the testes after administration of ^{131}I therapy for ablation of post surgical thyroid remnant in adult patients with differentiated thyroid carcinoma (Ceccarelli et al., 1999), but evidence has been presented that the radiation dose absorbed by testes after a single ablative dose of radioiodine is well below that associated with damage of seminal epithelium. No evidence of infertility has recently been reported in a large study on 122 men treated with radioiodine for differentiated thyroid carcinoma. Moreover, no major malformations have been reported in 106 children generated by 59 male patients previously treated with ^{131}I for differentiated thyroid carcinoma (Hyer et al., 2002). At the moment there are no adequate data on putative damage of testicular function in children and adolescents treated with ^{131}I.

Amenorrea with increasing serum FSH and LH concentration has been described in 1/3 of women shortly after radioiodine therapy. This is usually transient and appears to be related to the amount of ^{131}I administered (Vini et al., 2002). An earlier onset of menopause (in the range of 12 months) in women with differentiated thyroid cancer treated with ^{131}I during their childbearing age has been reported with no apparent relation to the radioiodine administered dose. At present there are no adequate data on male and female gonadal failure in patients with differentiated thyroid cancer treated with radioiodine during their childhood or adolescence (Ceccarelli et al., 2001).

The genetic effects of ^{131}I have been evaluated by assessing the outcomes of pregnancies and the health status of children in patients with differentiated thyroid carcinoma, who were treated with radioiodine. In one large European study (Schlumberger et al., 1996), the outcomes of 290 pregnancies occurring in females previously treated with ^{131}I for differentiated thyroid carcinoma were compared to those of 2181 pregnancies that occurred before ^{131}I treatment. The data indicated that the exposure to ^{131}I radiation did not alter the likelihood of stillbirth, congenital malformation, death during the first years of life, thyroid disease or other non thyroidal malignancies in the offspring. The only relevant finding was a relatively frequent occurrence of miscarriage (4 out of 10 cases) in the women who became pregnant within one year after treatment with ^{131}I. The question whether this was related to the ^{131}I irradiation or to the destabilized control of the hormonal status remains to be solved.

With respect to radioiodine treatment, early and late side-effects may be summarized as follows:

Early side-effects:

- Short-term gastritis after oral administration of ^{131}I (frequent)
- Radiation-induced sialadenitis (frequent)
- Local inflammation of thyroid remnant and remnant tumour tissue respectively or of distant metastases (seldom)
- Temporary thrombo- and leucopenia (frequent)
- Temporary oligospermia (frequent).
- Transient amenorrhoea or menstrual irregularities lasting up to 10 months (observed in 17% of patients)

Late side-effects:

- Sicca-syndrome due to radiation induced sialadenitis in 20-30% of the patients
- Pulmonary fibrosis in approximately 1% of patients with pulmonary metastases taking up radioiodine
- Radiation induced leukaemia in approximately 1% of the patients if substantial total doses delivered to the bone marrow (mean latency 5 years) – based on radiation-induced leukaemia in other than Chernobyl populations.
- Permanent infertility due to azoospermia theoretically possible in some 5% of patients, but existing evidence is not consistent. Because of the considerable risk of testicular damage, sperm banking seems to be advisable in young men likely to receive cumulative activities of 17 GBq and more.

Prognosis

In general, prognosis for young patients with papillary thyroid carcinomas that developed after the Chernobyl accident is excellent, but more studies are needed to evaluate the prognosis for children with distant metastases (Leenhardt and Aurengo, 2000). Further research is needed to develop prognostic criteria, including those based on molecular pathology tests, clinical manifestations and course of disease. The group from Ohio State University (Mazzaferri and Kloos, 2001) reported 40-year recurrence rates for thyroid cancer in the U.S. to be about 35%, two thirds of which occurred within the first decade after initial therapy. These rates, including those for distant recurrence, were higher for patients under age 20 and over 60 years. Thirty-year cancer mortality rates were about 12% with local recurrence and 43% with distant recurrence (p=0.001). Local disease comprised 68% of the recurrences in this study; among the 170 patients in whom the exact site of local recurrence in the neck soft tissues (30%) compared with those in cervical lymph nodes or the contralateral thyroid (16%, $p<0.05$). Distant metastases, mostly to the lungs, comprised 32% of the recurrences; after 40 years of follow-up half have died of cancer. The authors list factors predictive of high and low risks (Table 8).

Table 8. Risk stratification of variables influencing thyroid cancer recurrence and cancer death. Adopted from (Mazzaferri and Kloos, 2001)

Factors predictive of high risk	Factors predictive of moderate-to-low risk
Patient variables Age <15 yr or >45 yr Male sex Family history of thyroid cancer	Age 15–45 yr Female sex No family history of thyroid cancer
Tumour variables Tumour >1 cm in diameter in children Tumour >4 cm in adults	Tumour <4 cm in diameter
Bilateral disease	Unilateral disease
Extra-thyroidal extension	No extra-thyroidal extension
Vascular Invasion (both papillary and follicular thyroid cancer)	Absence of vascular invasion
Cervical, or mediastinal lymph node metastases	No lymph node metastases
Certain tumour subtypes: Hürthle cell, tall cell, columnar cell, diffuse sclerosis, insular variants	Encapsulated papillary thyroid carcinoma, papillary micro-carcinoma, cystic papillary thyroid carcinoma
Marked nuclear atypia, tumour necrosis, and vascular invasion (i.e. histological grade)	Absence of nuclear atypia, tumour necrosis, and vascular invasion
Tumours or metastases that concentrate radioiodine poorly or not at all	Tumours or metastases that concentrate radioiodine well
Distant metastases	No distant metastases

A retrospective analysis in 114 children and adolescents from Germany (Farahati et al., 1997) revealed distant metastases in 29 patients (25%). Using multivariate statistical methods, the influence of different risk factors associated with distant metastases has been studied: Tumour stage had the highest impact ($p=0.02$). There was a tendency to a higher rate of distant metastases in younger children; this effect, however, was only marginally significant ($p=0.08$). These data are consistent with the U-shaped frequency distribution of recurrences from differentiated thyroid cancer, where the peaks have been seen in young people below age 20 and in old patients above age 60 (Mazzaferri and Kloos, 2001). Lymph node metastases, which were frequent in the study on childhood thyroid cancer with 52%, did not have a negative impact on prognosis (Farahati et al., 1997).

In Belarusian children, who were younger at the time of the Chernobyl accident, there was a greater extra-thyroidal tumour extension ($p<0.02$) and more lymph node involvement ($p<0.001$) and tended to be associated with more distant metastases ($p=0.09$). Multivariate analysis revealed that younger age at the time of the accident ($p=0.001$) and advanced locoregional tumour extension (p<0.001) were the only significant factors influencing the risk for distant metastases of this malignancy (Farahati et al., 2000).

In general, the UICC tumour classifications (UICC 1997 and 2002) are problematic with respect to classification of T-staging in children (Farahati, Reiners, and Demidchik, 1999), since a fixed and not age - or thyroid volume related tumour diameter is the criterion for definition of stage T1. This problem became more marked with the new UICC classification of 2002 (UICC 2002), which increased the cut-off from 1.0 cm to 2.0 cm. Evidence based clinically relevant prognostic criteria derived both from clinical and molecular biology data should be developed for post Chernobyl thyroid cancer patients.

A group of 741 children treated in Minsk with total thyroidectomy (n=426) lobectomy (n=248) and subtotal thyroidectomy (n=48) was followed up for 1.5 – 220 months (mean: 96.6 months). Of the children, 80.8% were followed up for more than 5 years and 30.0% for more than 10 years. Recurrences were diagnosed in 204 (27.5%) cases, including 73 (9.9%) local relapses, 90 (12.1%) distant failures and a combination of local and distant failures in 41 (5.5%) patients. Multivariate logistic regression analysis revealed the following independent parameters significantly associated with the risk of lymph node failure: young age at diagnosis, multi-focal carcinomas, local lymph nodes involvement, and non-fulfilled ipsilateral or bilateral neck dissection. For lung metastases, significant risk factors were female gender, young age at diagnosis and a presence of symptoms. The observed five and ten years survival for the entire group was 99.3% and 98.5% respectively. Of 464 patients treated with ^{131}I, 336 (72.4%) children underwent ablation of thyroid remnants and 128 (27.6%) received radioiodine therapy for distant metastases. A complete response was achieved in 271 (58.4%) cases; in 159 (34.3%) cases stable partial response was observed and 34 (7.3%) patients were recognized as partial responders with still detectable ^{131}I accumulation in metastases but regressive serum thyroglobulin levels. Of 128 cases with lung metastases, complete, stable partial and partial response was documented in 37 (28.9%), 61 (47.7%) and 30 (23.4%) patients, respectively (Demidchik et al., 2005).

Non-cancer thyroid diseases

Relatively little has yet been published regarding thyroid outcomes other than thyroid cancer in Chernobyl populations, although one study has reported an elevated risk of benign thyroid tumours (Ivanov et al., 2003b). There is a particular concern for benign thyroid nodules and autoimmune thyroid disease, outcomes that have been associated with exposure to ionizing radiation in few studies of other radiation exposure circumstances (Ron et al., 1989; Schneider et al., 1993; Shore et al., 1993; Kerber et al., 1993). There have been reports of increases in autoimmune disease and anti-thyroid antibodies following childhood exposure to Chernobyl (Lomat et al., 1997; Pacini et al., 1999; Vermiglio et al., 1999; Vykhovanets et al., 1997; Vykhovanets, 2004). However, the Sasakawa Foundation study, which screened 114,000 children, found no association between a surrogate for thyroid dose (^{137}Cs in the body) and thyroid antibodies, hypothyroidism, hyperthyroidism, or goitre (Yamashita and Shibata, 1997). Additional data from high quality epidemiological studies are needed to clarify the relationship between benign thyroid diseases and exposure from Chernobyl (Eheman, Garbe, and Tuttle, 2003).

Nodular changes

The frequency of thyroid nodules detected by mass screening in populations afflicted by the Chernobyl accident varies between 1%-18%, and usually not more than 10% of those nodules are malignant (Nagataki, 2002). An ongoing cohort study is being conducted in Belarus and

Ukraine that includes 25,161 subjects under the age of 18 years in 1986 who are being screened for thyroid diseases every two years. While the primary objective is to examine the relationship between exposure to radioactive fallout from the Chernobyl accident and the risk of thyroid cancer, this epidemiological study is designed to estimate the risk of thyroid disorders including benign nodules and other disorders (Stezhko et al., 2004). Analyses are in progress.

From a clinical viewpoint, the methods for differential diagnosis of nodular thyroid lesions should be refined (e.g. by use of colour Doppler and 3D-ultrasonography, by improvement of cytology-/cytochemistry-techniques). For the future, follow-up programmes for especially young patients with thyroid nodules should be developed. Measurements of nodular volume by three-dimensional ultrasonography are more accurate, showing lower intra-observer variability and higher repeatability than achievable when made by two-dimensional conventional ultrasonography with less dependence on nodule size and echographic characteristics (Lyshchik, Drozd, and Reiners, 2004; Lyshchik et al., 2005). In this context, the efficacy of different medications (iodine, LT_4) for suppression of nodular growth should be tested.

Thyroid autoimmunity and thyroid function

Reports of increased rates of thyroid disease in populations exposed to radiation as a result of the Chernobyl accident have increased awareness and concern about the risk of autoimmune-related thyroid disease possibly associated with environmental radiation exposure. While the association between thyroidal irradiation and an increased risk of thyroid neoplasm is well established, much less attention has been devoted to the potential effects of environmental irradiation on the function of the thyroid. The information available to date is rather inconsistent. Earlier reports indicated increased risk of benign thyroid disease in children and adolescents of Kaluga cohort with ERR/1Gy of 0.2 (CI 0.06–0.34) (Ivanov et al., 1997). The UNSCEAR 2000 report did not indicate existing evidence of such associations (UNSCEAR, 2000). However, since 2000, new studies have been published that appear to link radiation exposure to an increased risk of thyroid dysfunction.

Drozd et al. (2003) screened the thyroid status in children exposed to ionizing radiation *in utero* and in the first year of life, comparing 328 children from Khoiniki region (Gomel province) who were exposed to radiation in April/May 1986 to 99 children from Braslav region (Vitebsk province) as controls. In 3.7% of the exposed children, solid thyroid nodules were found, compared to 3.1% cystic nodules in the controls. Autoimmune thyroiditis was detected in 1.8% of the exposed and 2% of the control children. Children exposed in the first trimester *in utero* had significantly smaller average thyroid volumes compared to those exposed in the third trimester. On average, TSH-levels were significantly higher in subjects exposed in the first trimester than that in the controls.

Eheman et al. (2003) reviewed published studies that evaluate the possible association between environmental thyroidal radiation and the presence of anti-thyroid antibodies as well as autoimmune thyroid disease (hypothyroidism and hyperthyroidism). They concluded that although some epidemiological evidence of an association exists, long-term, well-designed studies are needed in order to accurately evaluate the complex association between low-dose environmental radiation exposure and clinically significant non-neoplastic thyroid disease. The results of these studies will be important in determining the appropriate clinical follow-up of persons exposed to environmental thyroidal irradiation.

Expert assessment (clinical aspects)

Consensus

There is no doubt that thyroid cancer in children increased considerably in regions of Belarus and the Ukraine contaminated most heavily after the Chernobyl reactor accident. Typically, papillary thyroid carcinoma is prevalent in more than 90% of these children of young age. At the time of diagnosis, many children present with extraglandular tumour spread, lymph node and distant metastases.

Even in children with advanced tumour stages, treatment with thyroidectomy, followed by high-dose radioiodine therapy and consecutive levothyroxine TSH-suppressive hormone replacement is effective. In general, the prognosis for young patients with papillary thyroid carcinoma can be considered as excellent.

Gaps in knowledge

Thyroid cancer in children is a rare disease, so the worldwide experience related to diagnosis, treatment and follow-up of this tumour disease is limited. Radiation induced thyroid cancers may be characterized by molecular finger prints (e.g. RET translocations). However, up to now it still remains unclear if findings described by several authors may be explained at least partially by the young age of the patients. Iodine deficiency, which has been prevalent in some of the regions most heavily contaminated by Chernobyl fallout, may have increased radiation sensitivity and effects. On the other hand, high doses of stable iodine administered too late for blockade of radioiodine uptake may have increased radiation doses. Up to now, our knowledge about the natural course of radiation induced thyroid carcinoma is sparse. In children with disseminated lung metastases of papillary carcinoma e.g., the course of the disease after radioiodine therapy even in cases of still existing lung metastases may be favourable. Concerning the side-effects of treatment, our knowledge about the consequences of hypoparathyroidism frequently accompanying thyroidectomy is limited. Only few data are available about the late side-effects of high-dose radioiodine therapy and lifelong TSH-suppressive levothyroxine medication.

Conclusions (clinical aspects)

Radiation-induced thyroid disorders other than thyroid carcinoma, including benign thyroid nodules, non-autoimmune thyroid hypothyroidism and autoimmune thyroiditis have been reported after environmental exposure to radioisotopes of iodine. The information available to date with regard to thyroid function abnormalities and development of thyroid nodules as the result of the Chernobyl accident is rather inconsistent. While some epidemiological evidence of an association with thyroid autoimmune reactions (possibly transient) has been obtained, long-term studies are needed in order to evaluate possible association between environmental exposure and non-neoplastic thyroid diseases.

Recommendations (clinical aspects)

Improvement should be made in diagnostic techniques for differential diagnosis of benign/malignant nodules.

The UICC/TNM staging system should be adapted to childhood thyroid cancer.

Measures for prevention of complications of thyroidectomy should be developed.

Techniques for dosimetry and definition of optimal doses for radioiodine therapy in metastatic thyroid cancer should be developed.

Optimal therapeutic regimens for prevention of pulmonary fibrosis induced by radioiodine therapy should be developed.

Optimal regimens for age-related TSH-suppressive thyroid hormone therapy should be defined.

Optimal regimens for controlling permanent post-surgery hypoparathyroidism should be developed.

Long-term follow-up studies are needed to develop prognostic indicators related to tumour biology and treatment.

Long-term follow-up studies are needed of side-effects of radioiodine therapy in children and adolescents including secondary cancers and fertility.

Protocols on the use of rhTSH as a means for avoiding the impact of iatrogenic hypothyroidism in children and adolescents should be developed.

Screening programmes and controlled studies should be performed to ascertain the incidence of nodular thyroid disease, thyroid autoimmunity and thyroid dysfunction in populations exposed and not exposed to radiation after the Chernobyl accident.

Long-term follow-up studies of subjects developing benign thyroid diseases will be useful for the analysis of the biological behaviour of post Chernobyl thyroid dysfunctions. A comparison with the behaviour of the naturally occurring thyroid diseases will be of great interest.

Large-scale studies should be performed on the thyroid function of exposed populations to establish the incidence of hypothyroidism (and hyperthyroidism) and the relationship with thyroid autoimmunity.

Training programmes dedicated to clinicians should be set up for the use of new imaging techniques such as three-dimensional ultrasound and PET for a better definition of thyroid morphology, ultrasound pattern, nodular size and features.

Chapter 4

LEUKAEMIA

An elevated risk for leukaemia was recorded among the survivors of the atomic bombings of Hiroshima and Nagasaki (Preston et al., 1994). Ionizing radiation is a well substantiated causal mechanism for leukaemia other than chronic lymphoid leukaemia (CLL), with a latency period of 2-5 years following exposure. Leukaemia has also been associated with occupational exposure to radiation in early radiologists and radiation scientists (Yoshinaga et al., 2004) and radiotherapy for malignant and non-malignant diseases (Ron, 2003). The risk for leukaemia caused by low dose/low dose-rate exposures is not established. In the Utah case-control study on leukaemia in the U.S., a weak association between bone marrow dose from radioactive fallout from the Nevada Nuclear Test Site and all types of leukaemia, all ages, and all time periods after exposure was found (Stevens et al., 1990). In a pooled analysis study of nuclear workers from the U.S., Canada and the U.K., a statistically significant association was found for leukaemia excluding CLL (Cardis et al., 1995).

Exposure In Utero

Current status of evidence

Several ecological studies have addressed the question of leukaemia risk in children who were exposed to Chernobyl fallout while *in utero*, with conflicting results. A Greek study comparing rates for temporal cohorts born during "exposed" and "unexposed" periods found a 2.6-fold increase in leukaemia risk and elevated rates for those born in regions with higher levels of radioactive fallout (Petridou et al., 1996). However, the numbers of cases in each exposure group were small, and the results could not be duplicated when a similar approach comparing areas with the same categories of contamination (< 6 kBq/m^2, 6-10 kBq/m^2, > 10 kBq/m^2) was applied to the analysis of data from the German Childhood Cancer Registry (Steiner et al., 1998).

In a study in Belarus (Ivanov et al., 1998), where levels of contamination are higher by a factor of 10 or more, the results were similar to the Greek study but the trend was weaker, raising doubt about the role of radiation in the observed increase. Nevertheless, the highest annual incidence rate was in 1987, the year after the accident, and though numbers are small and the results statistically non-significant, the largest rate ratio (RR=1.51; 95% CI 0.63–3.61) was found in the two most contaminated regions (Gomel and Mogilev).

A more recent small study published by Noshchenko et al. (2001) compares leukaemia incidence during 1986 to 1996 among children born in 1986 and thus exposed *in utero* in Zhitomir, a contaminated oblast, with children born in Poltava, a supposedly uncontaminated oblast. The reported risk ratios based on cumulative incidence show significant increases for all leukaemia (RR=2.7; 95% CI 1.9–3.8) and for the subtype of acute lymphoblastic leukaemia (RR=3.4; 95% CI 1.1–10.4). The small number of cases (21 in Zhitomir, 8 in Poltava) suggests that interpretation of this result must be cautious.

An ongoing study, the European Childhood Leukaemia-Lymphoma Incidence Study (ECLIS) established in 1988 (Parkin et al., 1996), examines risk of leukaemia by age using data from population-based cancer registries in Europe (including Belarus and Ukraine). Focusing on the risk of leukaemia by age of diagnosis (six months intervals) in relation to the estimated doses from the Chernobyl fallout received *in utero*, preliminary results suggest a small increase in risk in infant leukaemia and leukaemia diagnosed between 24-29 months. Various sensitivity analyses examining potential sources of bias, especially differential availability of day/month of birth and diagnosis, showed a similar increase in risk for the aforementioned age-groups (Loos, 2004).

Expert assessment

Consensus

The available evidence from ecological studies is not entirely convincing, particularly in light of the results from Belarus. The statistical power of these studies was low for detecting moderate sized effects, and the exposure assessment measures were quite crude. There are as yet no data from analytical epidemiological studies in which individual dose estimates are available. Thus, there is neither strong evidence for or against an association between *in utero* exposure to Chernobyl fallout and an increased risk of leukaemia. The hypothesis that low-dose fetal irradiation may damage hematopoiesis processes still seems worth further testing, but primarily on the basis of biological assumptions related to susceptibility rather than to empirical evidence.

Based on studies of exposure to x rays (Bithell and Stewart, 1975; Wakeford and Little, 2003), it appears that the prenatal period is one of increased susceptibility to radiation damage. However, few data are available to assess this possibility in the context of the Chernobyl accident, although the observation that those youngest at the time of exposure are at highest risk is suggestive.

With respect to the observed temporal patterns, increases seen within 3-5 years of exposure are compatible with leukaemia increases in other exposure circumstances, including at Hiroshima and Nagasaki. Study of atomic-bomb survivors found increases in risk among those exposed *in utero* (Yoshimoto et al., 1991), but there was low power to evaluate whether the *in utero* period is more or less radiosensitive than the early postnatal period. Moreover, the exposure involved a substantially higher dose and dose rate. At the Nevada test site the numbers of cases among the *in utero* exposed were also too few to evaluate risk (Stevens et al., 1990).

Gaps in knowledge

The primary gaps in knowledge from the epidemiological point of view relate to the complete absence of analytical studies in which dose and risks are estimated at the individual level. However, because of the relatively small doses, and rarity of leukaemia as an outcome, it is not clear that such studies would have sufficient statistical power to yield meaningful results.

Recommendations

We know of no ongoing studies of *in utero* exposure and leukaemia risk. We recommend an extension of existing or planned analytical studies of childhood leukaemia to collect the necessary data to allow for the analysis of *in utero* exposure.

Exposure of Children

Current status of evidence

Several ecological epidemiological studies have examined the association between radiation exposure to children from Chernobyl and the occurrence of leukaemia. The European Childhood Leukaemia–Lymphoma Incidence Study (ECLIS) is one of the largest and most comprehensive to date. This study utilized incidence data in children under age 15 from 36 cancer registries in 23 countries. Average radiation doses were calculated based on estimates of environmental contamination and consumption of contaminated foodstuffs. Parkin et al. (1993) compared acute leukaemia incidence rates before the Chernobyl accident (1980-1985) with those for the years 1987 and 1988. Although the number of leukaemia cases for 1987-1988 significantly exceeded the number of cases expected on the basis of 1980-1985 data, there was no evidence that the excess in leukaemia rates was more pronounced in areas that were most affected by Chernobyl-related ionizing radiation exposure. Similar results were observed in the 5-year ECLIS follow-up report (Parkin et al., 1996).

Additional reports have focused on changes in childhood leukaemia rates before and after the accident in individual European countries and elsewhere. Overall, there was little evidence for an increase in rates of childhood leukaemia in Ukraine (Prisyazhiuk et al., 1991), Belarus (Ivanov et al., 1993; Gapanovich et al., 2001), Russia (Ivanov, 2003; Ivanov and Tsyb, 2002; Ivanov et al., 2003c), Finland (Auvinen et al., 1994), Sweden (Hjalmars, Kulldorff, and Gustafsson, 1994; Tondel et al., 1996), or Greece (Petridou et al., 1994; 1996) after the Chernobyl accident. Furthermore, there was no association between the extent of contamination and the increase in risk in these countries. However, one Swedish study (Hjalmars et al., 1994) reported a non-statistically significant yet suggestive increase of acute lymphocytic leukaemia risk in children younger than 5 at the time of exposure (OR 1.5; 95% CI 0.8–2.6). A small study in northern Turkey showed that in one pediatric cancer treatment center, more patients with acute lymphocytic leukaemia were seen after the accident than before, but no incidence rates were reported (Gunay, Meral, and Sevinir, 1996).

There has been only one analytical (case-control) study of childhood leukaemia reported to date (Noshchenko et al., 2002), based on cases identified among residents of the Rivno and Zhytomir oblasts in Ukraine. Cases were under age 20 at the time of the accident and were diagnosed between 1987 and 1997. Data were collected on 272 cases, however, the analysis was based on only 98 cases that were independently verified and interviewed. Controls were randomly selected from the same oblasts, excluding the raion of residence of the case, and matched according to age at the time of the accident, gender, and type of settlement. The mean estimated dose to the bone marrow among study subjects was 4.5 mSv and the maximum was 101 mSv. The study found a statistically significant increased risk of acute leukaemia among males with cumulative doses above 10 mSv and diagnosed from 1993-1997. A similar association was found for acute myeloid leukaemia diagnosed in the period 1987-1992. These results should be interpreted cautiously, however, as they are based on approximately only one-third of the cases and a lesser proportion of controls, and it is not clear whether cases and controls were selected for dose estimation in an unbiased manner.

There are several ongoing studies of childhood exposure and leukaemia for which results are not currently available. These include:

- International Consortium for Research on the Health Effects of Radiation case-control study of childhood leukaemia in Ukraine, Belarus, and Russia.

- Franco-German study of leukaemia incidence in children in Bryansk and Kaluga
- Franco-German study of leukaemia incidence in children in several oblasts in Ukraine.

Expert assessment

Consensus

On balance, the existing evidence does not support the conclusion that rates of childhood leukaemia have increased as a result of radiation exposures from the Chernobyl accident. However, ecological studies of the types conducted to date are not particularly sensitive to detecting relatively small changes in the incidence of a disease as uncommon as childhood leukaemia over time or by different geographical areas. Further, existing descriptive studies vary in several aspects of study design: methods of case ascertainment (cancer registries versus retrospective record review), methods of classifying radiation exposure, and length of follow up after the accident (range 2–10 years). The single analytical study is insufficient to draw convincing conclusions regarding leukaemia risk among children after Chernobyl exposure.

Gaps in knowledge

As yet, there is no convincing evidence to demonstrate a measurable increase in risk of leukaemia following childhood exposure from Chernobyl. Thus, the primary gap in knowledge is the existence or nonexistence of a measurable risk. Other factors such as the dose-response relationship, the effect of protracted exposure, potential modifying effects of age at exposure and time since exposure are also unknown, and study of such effects is contingent upon the basic demonstration of a measurable risk. However, the statistical power for testing for a measurable association will generally be low, and the power for modifying effects will be lower still.

Recommendations

Incidence rates for childhood leukaemia in populations exposed to Chernobyl radiation should continue to be monitored in order to detect increases that may still occur.

Properly designed and executed analytical epidemiological studies with individual dose measurements and individual risk estimation should be encouraged, as these will give the most definitive results with respect to this important issue.

Exposure of Adults

Studies of liquidation workers

Reports of leukaemia in adults exposed to radiation from Chernobyl have focused largely on individuals involved in clean-up operations after the accident.

An initial analysis of a cohort of 143,032 liquidation workers from Russia after nine years of follow-up revealed SIRs of 113 (95% CI 62–190) and 177 (95% CI 122–247) for the observation periods 1986-1989 and 1990-1993, respectively (Ivanov, 1996). An excess relative risk (ERR) of 4.30 per Gy was estimated from this study. Shantyr et al. (1997) investigated 8,745 Russian recovery operation workers involved in operations from 1986 to 1990. Radiation doses ranged from 0–250 mSv. Although cancer incidence increased, particularly 4–10 years after the accident, no evidence of a dose-response relationship was found. Similarly, Tukov and Dzagoeva (1993) observed no increased risk of hematological diseases, including acute forms of leukaemia, in a study of Russian recovery operation workers and workers from the nuclear industry. More recently, Ivanov et al. have found an approximately two-fold increased incidence of leukaemia (excluding chronic lymphocytic leukaemia) among Russian liquidation workers with estimated total doses of 150–300 mGy (Ivanov et al., 2002; 2003c; 2003d).

Buzunov et al. (1996) investigated the health status of 174,812 Ukrainian recovery operation workers (96% males), the majority (77%) of whom were exposed in 1986 and 1987 (Buzunov et al., 1996). The average rate of leukaemia among the male recovery operation workers was 13.4 per 100,000 person-years among those employed in 1986 and 7.0 per 100,000 person-years among those employed in 1987. Eighteen cases of acute leukaemia among workers with doses between 120–680 mGy occurred between 2.5 and 3 years after exposure in 1986-1987. However, no apparent trend over time was seen among those employed in 1986.

An analysis of the mortality and cancer incidence of 4,833 Chernobyl recovery operation workers from Estonia found a non-statistically-significant excess of non-Hodgkin's lymphoma, based on three cases, and no cases of leukaemia (Rahu et al., 1997). However, the study was limited by the relatively small size of the population and a relatively short follow-up period.

There has been only one case-control study of liquidation workers published to date, nested within the cohort from the Russian National Medical and Dosimetry Registry (Konogorov et al., 2000). A total of 34 non-CLL cases of leukaemia were identified, diagnosed between 1986 and 1993. Four controls were chosen for each case, matched according to age and region of residence at diagnosis. The mean dose for cases was 115 mGy and for controls 142 mGy. Although the estimated relative risks were elevated for workers with the highest exposures, e.g., those who spent the most time in the Chernobyl exclusion zone (RR=3.07; 95% CI 0.71–13.24) or those exposed to the highest dose of radiation (RR=3.70; 95% CI 0.70–19.66), these were not statistically significant.

Studies of the general population

A few studies have investigated populations living in highly contaminated areas. Osechinsky et al. (1995) investigated the incidence of leukaemia and lymphoma in the general population of the Bryansk region of the Russian Federation for the period 1979-1993 using an *ad hoc* registry of hematological diseases established after the Chernobyl accident. The incidence rates in the six most contaminated districts (more than 37 kBq/m^2 of ^{137}Cs deposition density) did not exceed the rates in the rest of the region or in Bryansk city, where the highest rates were observed. Comparisons of crude incidence rates before and after the accident (1979-1985 and 1986-1993) showed a significant increase in the incidence of all leukaemia and non-Hodgkin's lymphoma, but this was mainly due to increases in the older age groups in rural areas. The incidence of childhood leukaemia and non-Hodgkin's lymphoma was not significantly different in the six most contaminated areas from the incidence in the rest of the region. Similarly, Ivanov et al (1997) found no evidence of an increase in leukaemia rates in the most contaminated areas of the Kaluga district of the Russian Federation after the Chernobyl accident.

In Ukraine, Bebeshko et al. (1997) examined incidence rates for leukaemia and lymphoma in the most highly contaminated areas of the Zhytomir and Kiev districts before and after the Chernobyl accident. Total incidence in adults increased from 5.1 per 100,000 during 1980-1985 to 11 per 100,000 person-years during 1992-1996, but there was no excess in contaminated areas of the regions. Likewise, no excess cases were found among children who resided in contaminated districts. Similarly, Prisyazhniuk et al. investigated the incidence of leukaemia and lymphoma in the three most contaminated regions of Ukraine (Prisyazhniuk et al., 1995). There was a steady increase in leukaemia and lymphoma rates for both men and women between 1980 and 1993, but there was no evidence of a more pronounced increase after the accident.

On-going studies

There are several on-going studies of adult exposure and leukaemia risk for which results are not currently available. These include:

- Ukrainian-American study of leukaemia and related diseases in clean-up workers
- IARC case-control study of leukaemia and non-Hodgkin's lymphoma risk among liquidators in Belarus, Russia, and Baltic Countries
- Franco-German study of leukaemia incidence in adults in Bryansk and Kaluga
- Franco-German study of leukaemia incidence in adults in several oblasts in Ukraine

The IARC case-control study of leukaemia and non-Hodgkin's lymphoma (Kesminiene et al., 2002) has a design similar to that of the study of thyroid cancer risk among Chernobyl liquidators described above and is nested within the same cohort of 146,000 liquidators from Belarus, Russia and Baltic countries. The objectives of this study were to estimate the radiation induced risk of these diseases among liquidators of the Chernobyl accident, and, if possible, to study the effect of exposure protraction and radiation type on the risk of radiation induced cancer in the low to medium (0–500 mSv) radiation dose range. Overall, 117 cases and 481 controls have been included in the study. An international panel of haematologists and pathologists has reviewed diagnoses. Data collection is complete. Individual estimates of kerma in air and of dose to the bone marrow were derived for each subject in the study, using a method of analytical dose reconstruction (RADRUE) developed within the study. Doses were reconstructed and risk analyses are underway. The first results of these studies are expected shortly. The estimation of uncertainties in doses and the evaluation of their impact on risk estimates will continue through 2005.

Expert assessment

Consensus

Conclusions regarding whether there is evidence of an increased risk of leukaemia associated with exposure to radiation from Chernobyl are different for liquidation workers and the general population. On balance, there is no convincing evidence that the incidence of leukaemia has increased in adult residents of the exposed populations that have been studied in Russia and Ukraine. However, few studies of the general adult population have been conducted to date, and they have employed ecological designs that are relatively insensitive.

In liquidation workers, initial studies revealed little increase in the incidence of leukaemia associated with Chernobyl radiation exposure. However, the most recent studies suggest a two-fold increase in the incidence of non-CLL leukaemia between 1986 and 1996 in Russian liquidation workers exposed to more than 150 mGy (external dose). On-going studies of liquidation workers are expected to provide additional information on the magnitude of a possible increased risk of leukaemia, based on individual estimates of radiation dose.

Gaps in knowledge

Although there is currently no evidence to evaluate whether a measurable risk of leukaemia exists among those exposed as adults in the general population, the possibility of conducting studies of such adults with adequate power seems remote, so that risk estimates in the future will have to be based upon sources other than direct observation of the Chernobyl population.

With regard to liquidators, there is clearly a need to clarify the existing observations that have been reported indicating a possible relationship. Further studies will have to focus on such methodological improvements as refining dose estimates, obtaining independent confirmation of diagnoses and then estimating more specifically the nature of the dose response, in particular, evaluating as far as possible dose and dose-rate effectiveness factors by comparison with studies conducted in other populations with differing doses and dose rates.

Recommendations

Whereas it is recognized that additional ecological studies will be carried out, well designed analytical studies with individual radiation dose estimates will be needed to provide more definitive information on the magnitude of the risk of leukaemia in relation to radiation exposure from Chernobyl, and the nature of any dose response.

Large-scale analytical studies of liquidation workers should be continued to investigate the incidence of leukaemia and temporal changes in risk associated with Chernobyl radiation dose. Combined analyses of analytical studies of leukaemia among liquidators from different countries should be considered where feasible in order to improve the power to detect an effect, if it exists, and the precision of risk estimates.

Decisions regarding whether to conduct additional studies of the incidence of leukaemia in adult residents from exposed populations should await the results of ongoing studies.

Chapter 5

SOLID CANCERS OTHER THAN THYROID

Background

Cancer, as a whole, is one of the commonest forms of disease affecting humans, both in terms of incidence and mortality. There were approximately 10 million new cases of cancer and six million deaths from cancer reported worldwide in the year 2000 (IARC, 2000).

In general, the factors that cause cancer differ widely depending on the specific cancer being considered, though some causative factors, e.g. smoking, are known to cause a number of different cancers. Similarly, ionizing radiation is known to cause most types of cancers, though the sensitivity of different organs to radiation-induced cancer differs considerably and for some organs it is not clear whether or not that particular organ is susceptible to radiation carcinogenesis.

In considering the effect of radiation on cancer risk, it is customary to consider leukaemia (and, occasionally, other cancers of the lymphatic and haematopoietic system) separately from other cancers (the “solid” cancers). This is because leukaemia and solid cancers differ considerably in their sensitivity to radiation in terms of the minimal latency period, the time dependency of risk and the dose-response relationship.

For solid cancers, the current dose-response model which appears to fit the data well at moderate to high doses is a simple linear function of dose, although the possible existence of a threshold effect or curvilinearity at very low doses is still a matter of some dispute (Pierce et al., 1996; Ron et al., 1998; Hoel and Li, 1998). On a relative risk scale, those exposed at young ages appear to be more susceptible than those exposed at older ages, and women are more susceptible than men, although such differences are less clear when considering excess absolute risks. Although it is clear that the sensitivity to ionizing radiation (i.e., the slope of the dose-response relationship) differs by organ, it has been argued on statistical grounds that it may be more appropriate to consider solid cancers as a group when estimating risk from ionizing radiation (Pierce and Vaeth, 1991; Pierce and Preston, 2000).

One important caveat should be borne in mind when considering evidence of increases in solid cancers among Chernobyl-exposed populations. The typical minimal latency period for solid cancers seen in high-dose studies is of the order of ten-fifteen years, so no increase in risk for solid cancers would be expected to manifest itself until the end-1990s at the earliest. Thus, if solid cancers are to occur from Chernobyl radiation exposure, they would only now begin to appear.

Current Status of Evidence

Few additional studies of non-thyroid solid cancers have been published since the UNSCEAR 2000 report, which concluded that the occurrence of radiation-related solid tumors, other than thyroid cancers, in workers or in residents of contaminated areas have not so far been observed. New studies that have been published after 2000 have not modified this conclusion.

The next several paragraphs describe the results that have been published since UNSCEAR 2000.

All solid cancers combined

General population

No new analyses of overall non-thyroid solid cancer incidence or mortality in general populations or cohorts, e.g. residents of contaminated areas, have been published in the peer reviewed scientific literature since UNSCEAR 2000.

Liquidation workers

Ivanov et al. (2004b) examined a cohort of 55,718 Russian liquidation workers who worked within the 30-km zone during 1986-1987, and who have documented external dose estimates ranging from 0.001 to 0.3 Gy (mean 0.13 Gy). A total of 1370 solid cancer cases were diagnosed during 1991 to 2001 (including 43 thyroid cancer cases). They reported slight increases of cancer incidence in this cohort during the periods 1991-2001 (ERR/Gy = 0.33; 95% CI -0.39–1.22) and 1996-2001 (ERR/Gy = 0.19; 95% CI -0.66–1.27) compared to an internal control group, and noted that these results agreed well with those obtained in comparisons to population rates for Russia. This study was based on registry data without additional diagnostic confirmation, and therefore may include misdiagnosed cases, and be subject to underreporting due to false negatives. The possibility of screening bias cannot be excluded, although the similarity of comparisons to internal and external controls suggests that such bias had little impact if any.

In another paper, Ivanov et al. (2004a) reported similar findings from a study of 8,654 nuclear workers from the Russian National Medical and Dosimetric Registry (RNMDR) who participated in recovery operations at Chernobyl and who had documented external doses. For the period 1996-2001, they reported that the incidence of solid tumours was somewhat lower than that of the general Russian population (SIR=0.88; 95% CI 0.76–1.02), and estimated an excess relative risk due to Chernobyl radiation exposure of 0.95 per Sv. This excess was not statistically significant (95% CI -1.52–4.49), however, due to the comparatively modest size of the cohort and limited duration of follow-up, this cannot be interpreted as evidence against the existence of an increased risk. It should be noted that these subjects are entitled to special medical care and follow-up. Therefore, their diagnostic data are considered to be of high quality despite the absence of independent confirmation, and the likelihood of screening bias is less than for the larger cohort of liquidation workers described above.

Breast cancer

Breast cancer is of particular interest and concern because of its profound public health significance and its known susceptibility to induction by at least some types of radiation exposure. The relative risks of breast cancer for women exposed to external radiation in childhood and adolescence are among the highest known radiation related risks for any cancer type along with leukaemia and thyroid cancer. No descriptive or analytical epidemiological studies of breast cancer risk in populations exposed to radiation from Chernobyl have been published in the peer reviewed literature. However, one monograph report has cited elevated breast cancer incidence rates based on members of Ukrainian registries. These included 150,000 residents of contaminated areas close to Chernobyl; 90,000 liquidation workers in 1986 (with mean dose evaluated as 100–200 mSv) and in 1987 (mean dose 50–100 mSv); and 50,000 evacuees from Pripyat (mean dose 10–12 mSv) and the 30 km zone (mean dose 20–30 mSv) (Prysyazhnyuk et al., 2002). For breast cancer among the women in these cohorts, the standardized incidence ratio (SIR), based on comparisons to Ukrainian female population rates, was reported as 1.50 (95% CI 1.27–1.73) for the period 1993-1997 among residents of contaminated territories. For evacuees from the 30 km zone, the SIR during 1990-1997 was 1.38 (95% CI 1.06–1.70), and for women who served as liquidation workers during 1986-1987, who comprised only about 5% of the liquidation worker cohort, the SIR for the period 1990-1997 was 1.51 (95% CI 1.06–1.96). These registry-derived estimates must be interpreted with particular caution, since they were not subject to diagnostic confirmation and may be influenced by differences in screening intensity.

A descriptive epidemiological study has recently been carried out in Belarus and Ukraine, in collaboration with IARC and the Finnish Cancer Registry. Preliminary results of the study indicate a significant increase in the incidence of pre-menopausal breast cancer among women exposed before the age of 45 in the most contaminated districts (with an average lagged cumulative dose of 40 mSv or more) compared to less contaminated territories (IARC, 2005). Analyses take into account pre-existing trends in breast cancer incidence in these regions. These observations do not appear to be due to screening, as similar results are obtained for symptomatic and non-symptomatic breast cancer, as well as for both localized and non-localized tumours (Pukkala et al., 2006).

IARC and ICRHER have conducted preliminary studies demonstrating the feasibility of case-control studies of breast cancer among residents of contaminated regions of Belarus, Russia and Ukraine. Funding to support the conduct of such studies is currently being sought.

Other specific solid cancers

No descriptive or analytical epidemiological studies of non-thyroid solid cancer risk in relation to Chernobyl radiation have been published in the peer-reviewed literature. However, there has been a series of papers investigating aspects of possible radiation carcinogenesis in bladder or kidneys (Morimura et al., 2004; Romanenko et al., 2000; 2001; 2002; 2003).

Expert assessment

Consensus

To date, there has been relatively little study of the morbidity or mortality from solid cancers other than thyroid cancer in populations exposed to radiation from the Chernobyl accident. Therefore, it must be concluded that, while there is no evidence of increased risk of non-thyroid solid cancers resulting from Chernobyl, the possibility of such increased risk cannot be ruled out. If any increased risk does occur, it may be greatest in liquidation workers, especially those receiving the highest doses.

This conclusion is not surprising, given the likelihood that any excess in these diseases, if it is going to occur, would not be expressed or detectable until one or more decades after the accident. In addition, the comparatively low doses received by most residents of contaminated areas, and even, it appears, by many liquidation workers, make it likely that any increased risk of non-thyroid solid cancers will be small and difficult to detect even in large cohorts.

In the absence of evidence of Chernobyl-related increased risk of non-thyroid solid cancers, it is neither possible nor necessary to comment on such characteristics as the shape of a dose response, its variation over time, or the existence of dose effect-modifying factors. It is also not appropriate to speculate that, if risk has been increased or will be increased in the future, such characteristics will be similar to those seen in studies of other populations in which radiation-related increased risks have been observed. This is especially true for general populations of residents in contaminated areas, since there have been no definitive studies of other populations exposed to prolonged low-dose-rate environmental contamination.

The current absence of evidence of increased risk of non-thyroid solid cancers is not incompatible with the existing body of epidemiological evidence concerning risks of radiogenic cancer (see note below). There are two reasons for this. First, as mentioned above, the existing studies of Chernobyl's consequences suggest that doses were generally low, even for many liquidation workers. Moreover, less than two decades have elapsed since the Chernobyl accident, which may be too little time for the expression of radiogenic non-thyroid solid cancers. Thus, studies to date have probably had too little statistical power to detect the increased risks that may have occurred. Unfortunately, none of the publications of these studies have described their power, so it is not possible to assess their power with useful precision. Second, most of the existing epidemiological evidence is derived from studies of acute external exposure to relatively high doses or high dose rates, such as the mortality and incidence studies of Japanese atomic-bomb survivors.

Gaps in knowledge

To date there have been no definitive epidemiological studies of the impact of exposure to radiation from Chernobyl on the incidence of or mortality from non-thyroid solid cancers, either as a group or for specific organs. Therefore, it is unknown whether the incidence of or mortality from such cancers has been increased by that exposure. And of course, if incidence and/or mortality have increased, the magnitude of the increases, the nature of their dependence on radiation dose, and the modifying effects of other characteristics such as age and sex remain unknown.

The current knowledge concerning the effects of radiation on such cancers is based largely on acute external exposures to relatively high doses. Such exposures are quite different from those caused by Chernobyl, and consequently the extent to which risk estimates derived from them can be applied to the Chernobyl experience is unknown. This is particularly true for the populations that have lived in contaminated regions, which have accumulated radiation doses from both internal and external exposure at low dose rates over prolonged periods. However it is also true for liquidation workers. Even though many liquidation workers received higher doses than the general populations of contaminated regions, and at higher dose rates, their exposures were generally much less acute and more likely to include internal exposure than those of the Japanese atomic-bomb survivors or medically irradiated cohorts. Moreover many liquidation workers have also lived in contaminated regions and consequently accumulated additional radiation dose.

The initial ecological observations of an increase in the incidence of pre-menopausal breast cancer 10 years or more after the accident in women who were below the age of 35 at the time of the accident and resided in the most contaminated areas merits further research. A population-based case-control study in these areas would be of value to evaluate the existence of this risk and, if appropriate, the dose-response relationship and the effects of age at exposure. It is noted that, in populations with higher dose exposures such as the atomic-bomb survivors and patients with medical exposures, the risk of breast cancer among women exposed in childhood and adolescence is the highest risk of radiation induced cancer after those of leukaemia and thyroid cancer.

It may be some time before definitive epidemiological studies of other non-thyroid solid cancers are possible. As noted above, radiogenic solid cancers, i.e., the additional cancers that would not have occurred in the absence of the radiation exposure, may not be detected, i.e., may not grow to detectable size or cause death, until one or more decades after the exposure. Moreover, if any radiogenic solid cancers occur, they are likely to continue to be detected for decades after that minimum latency. In addition, if the organ doses are comparatively low on average and/or the incremental risk per unit dose is small, the number of radiogenic solid cancers will be small. Since the statistical power of epidemiological studies to detect increased incidence or mortality depends in large part on the number of radiogenic cases or deaths, it may be several more years before definitive epidemiological studies are possible.

Conclusions

From the above discussion and recommendations, the following conclusions may be drawn with regard to the impact of the Chernobyl accident on risk of solid cancers other than thyroid cancer on the populations of Belarus, the Russian Federation and Ukraine.

With regard to the dosimetry to be applied to liquidators, considerable caution should continue to be employed in the use of the “official” doses contained in the various state registries. This is due to inaccuracies in the doses, large uncertainties affecting many dose estimates and the variability of that precision according to the source of doses. The time and motion method of RADRUE described in Chapter 2 seems the best hope at present for constructing individual doses received by liquidators for use in analytical epidemiological studies. However, until more validation studies on the method are completed, caution must be used in applying the RADRUE method, again, because of uncertainty as to its accuracy and precision.

For doses applying to the general population, registries of such doses have been developed in Belarus, the Russian Federation and Ukraine. These can be adapted and applied to analytical and ecological epidemiological studies, though their use in studies conducted in one or more of these states must be treated with caution, because of uncertainty in the comparability of the different dose methodologies used.

Regarding cancers other than thyroid cancer, there remains a lack of positive evidence of any measurable effect of Chernobyl radiation apart, possibly, from pre-menopausal breast cancer in the general population and leukaemia among the liquidators. However, for most solid cancers, the minimal latency period is likely to be much higher than that for leukaemia, with current data suggesting a minimum of five years for breast cancer, and 10 or more years for the other cancers. Thus, it is possible that insufficient time has passed for a measurable risk to occur among those exposed with respect to these cancers. In addition, the low to moderate doses received and the lower risk per unit of dose for these cancers, compared to leukaemia, may introduce a lack of statistical power in current studies.

Overall, the additional data accumulated since the UNSCEAR 2000 report have not materially affected the conclusions of that report with respect to non-thyroid solid cancers. No definitive evidence of a measurable increase in risk has yet been reported.

It must be emphasized that the failure to observe a measurable increase in risk to date certainly does not imply that no increase in risk has occurred. Based on current scientific knowledge coming primarily from epidemiological studies conducted among different populations receiving much higher doses or higher dose rates, such as the atomic-bomb survivors study, most scientists would accept the fact that some increase in risk for those cancers that are radiosensitive has almost certainly occurred in the populations of Belarus, the Russian Federation and Ukraine. However, because doses were moderate or low and protracted, this has not manifested itself in the various epidemiological studies due to their lack of statistical power. The only sensible way to estimate those risks is to use extrapolations from observations made in studies conducted among high-dose populations. As discussed in Chapter 2, this involves a good deal of uncertainty in the various extrapolation factors. Thus, such risk projections should be treated with great caution, although they currently represent the best that can be done in estimating the burden of leukaemia and other cancers (excluding thyroid cancer) on the affected populations.

Another important point to be noted is that the low to moderate doses may have led to a small increase in the relative risk of the cancers concerned. However, given the large number of individuals exposed to such doses, the absolute number of cancer cases caused by a small increase in the relative risk would be substantial.

Finally, there remains the question of extrapolating into the future to estimate the number of cases that could occur due to the Chernobyl accident. This may be particularly important for public health planning purposes, but several caveats should be borne in mind. First, there is the uncertainty in extrapolating dose/risk models from one population to another. Second, any such models have considerable uncertainty in modeling the effect of time since exposure. Third, the doses to large groups of the population are still quite uncertain. These factors limit the accuracy and precision of projections. If such projections are made for public health reasons, it is essential that some measure of uncertainty be provided taking into account all the factors that are known to be uncertain such as those mentioned above. In particular, extrapolations should be limited to the relatively near future since the longer the period about which such projections are made, the greater the uncertainty.

In summary, the current situation in assessing solid cancers (other than thyroid cancer) risk from Chernobyl has not substantially changed since the UNSCEAR 2000 report. It is to be hoped that improved analytical epidemiological studies that take into account individual doses and are of sufficient size and sufficiently free from bias will shed more light on this very important public health and scientific question in the future.

Recommendations

Incidence of non-thyroid solid cancers in both general populations and cohorts of liquidation workers should continue to be monitored, through the existing cancer registries and other specialized registries such as the RNMDR or Ukrainian State registry of persons affected by the Chernobyl accident (National Registry of Ukraine Ministry of Health). Efforts to evaluate the quality of those registries and to reduce any deficiencies should be given high priority.

Registries in the different affected nations should develop and adopt common standards to enhance the comparability of the disease incidence data they report.

Future epidemiological studies of solid cancers in populations exposed to Chernobyl radiation should, whenever practical, examine risks of cancers in specific organs, rather than risk of all non-thyroid solid cancers combined. Analyses of combined cancer types are perhaps of some interest for public health planning purposes, and may be more feasible than site-specific studies due to the larger number of cases. However such studies are difficult to interpret, since different organs are likely subject to different risks of radiogenic cancer induction and may have differing levels of detection rates arising from variation of screening and detection modalities.

Regarding specific cancer types, the following solid cancers may be of particular interest for future study because of their public health significance, known susceptibility to induction by at least some kinds of radiation exposure, the existence of prior research related to Chernobyl: breast cancer, stomach cancer, lung cancer, and bladder and renal cancer.

In the future, epidemiological investigations of non-thyroid solid cancer risks should be based on analytical study designs whenever possible. The development in recent years of methods for estimating individual doses, including individual organ doses, as well as the uncertainties of those dose estimates, makes the conduct of analytical studies and the estimation of quantitative risk estimates quite practical.

Careful attention should be paid to dose estimation and accounting for the impact of dose uncertainties in all future studies.

Future studies should focus not only on risk estimation, but whenever possible should be designed to provide information that can be used to assess dose rate effects (e.g., by comparison with estimates of high dose rate effects), secular trends in radiogenic risk, and dose effect modification.

Chapter 6

NON-CANCER AND NON-THYROID HEALTH EFFECTS

Over the last two decades, a vast number of non-neoplastic health effects have been attributed to the Chernobyl accident. For this report, it was not possible to produce a scientific discussion, review current epidemiology, and make recommendations on all types of reported heath effects. The literature is vast and ranges from reports in the mass media and anecdotal cases in non-peer reviewed literature to large well conducted scientific studies. The expert group has, therefore, concentrated on 8 main topic areas that would affect a large number of persons and for which there might be a sufficient number of scientific studies. The expert group attempted to provide a consensus opinion and recommendations for the following:

- Cataracts
- Cardiovascular diseases
- Cytogenetic biomarkers and their significance
- Immunological system effects
- Heritable effects, birth defects and children's health
- Mental, psychological and central nervous system effects
- Estimation of mortality attributable to the Chernobyl accident
- Medical programmes and medical monitoring (screening)

The last two topics are presented in separate chapters that follow. The order in which the other topics are presented is not meant to imply their relative importance. Much of the data in some of these topic areas is of a descriptive nature and subject to the vagaries of case identification, non-uniform registration, variable or uncertain diagnostic criteria and uncertainties in uniformity of data collation. For incidence and mortality from a number of diseases, the expert group relied on official data supplied by members of the expert group who were representing Belarus, Russia and Ukraine.

In a number studies mentioned in the following sections, population statistics have been utilized. Such parameters are difficult to rely on in order to detect radiation effects unless the effects are large enough to be statistically discernable. Further, such data are inadequate for use in order to exclude completely the possibility of weak radiation effects. A major confounding factor in mortality studies has been the significant decrease in average lifespan in populations of all three affected countries. This has occurred even in uncontaminated regions. Over the last 15 years, the average lifespan for a male in Russia and Ukraine has decreased from over 70 to about 61 and from 67 to 61 years, respectively. This can be compared to Western Europe where the average lifespan is about 75 years for males. The effect of adverse economic circumstances and deterioration of the healthcare system remain largely unquantified. For a number of topic areas, the data are limited and are mainly available from only one of the three countries (e.g. liquidator mortality from Russia, malformations from Belarus and infant mortality from Ukraine). This also limits the certainty of conclusions.

The subject matter presented in this chapter is, therefore, less scientifically rigorous that that for the prior sections on leukaemia and thyroid studies. In contrast to neoplastic diseases, many of the entities presented here cannot be diagnosed with a similar degree of certainty. With the exception of cataracts, the diagnosis of many of the health effects was often made as a result of a clinical impression, and it is extremely unlikely that uniform diagnostic criteria were followed in such large populations in all three countries.

Many of the studies we reviewed report associations, but have not had sufficient control groups, statistical power or other characteristics necessary to allow arguments to be made for radiation causation. Results of a number of studies were presented to the expert group, but without the necessary supporting information to allow us to judge the scientific merits of the findings. In addition, most of the topic areas covered here have a wide variety of etiological agents that can produce significant bias in almost any of the studies. For example, smoking and alcohol consumption can cause a major increase in overall mortality and morbidity, an increase in neoplasms, and an increase in cardiovascular disease. We also realize that there may be significant overlap in the topics presented. For example, radiation related stress may lead people to smoke more, which, in turn, can lead to more lung cancer and cardiovascular disease without radiation having had any direct effect.

Finally, the group of health effects we have covered also varies significantly in their possible biological and mechanistic relationship to radiation dose. Cataracts, for example, are well known to be caused by damage to the cells of the lens of the eye, but these effects need to be carefully distinguished from senile changes. Mental health, stress and psychological effects are indirect and may occur as a result of perceived, and not actual, radiation exposure.

As a result of all the above issues, the conclusions of the expert group relative to most of the topics are sometimes more qualitative than quantitative in nature. With psychological issues we were able to conclude a major effect. In a number of areas we were able to conclude that the bulk of the data does not support a large or statistically significant effect. In some other areas, we did not have sufficient evidence to present an informed opinion. There remains an overall need to design future studies with extreme care in order to be able to obtain useful, unbiased and non-confusing information. The group also provided recommendations on the possible course of future actions.

The Eye and Cataractogenesis

Background

Of the ocular tissues, by far the most sensitive to ionizing radiation is the lens (Merriam, Jr. and Focht, 1957). Radiation can cause an opacification or cataract in the lens. Opacities in the lens of the eye differ widely in severity, from those causing no obvious decrease in visual acuity to those severe enough to cause significant visual impairment.

While not unique to radiation, radiation cataracts initially manifest as defects in the transparency of the posterior superficial cortex of the lens and is referred to as posterior subcapsular (PSC) cataract. It is critical in studies of purported eye exposure to recognize that PSC cataracts are, as Otake and Schull stated, the ultimate expression of radiation damage to the lens (Otake and Schull, 1982). Cataracts appear to develop some time after radiation exposure. The latency duration is dependent on the rate at which damaged epithelial cells undergo aberrant differentiation (fibregenesis) and accumulate in the PSC region (Worgul and Rothstein, 1975; Worgul, Merriam, Jr., and Medvedovsky, 1989; Merriam, Jr. and Worgul, 1983). It appears that up to a certain dose, the latency time to appearance is inversely related to dose. At higher doses, the cataract onset time cannot decrease further. As it relates to cataracts following the Chernobyl accident, the UNSCEAR 2000 report limits itself to the following statement: “Cataracts, scarring and ulceration are the most important causes of persistent disability in acute radiation sickness survivors.” (UNSCEAR, 2000).

Current status of evidence

There have been several studies undertaken regarding cataract formation in the populations exposed to radiation from the Chernobyl accident. Much effort has been focused on the first responders, who suffered acute radiation effects, and the liquidators involved in the extended clean-up and stabilization of the site (Junk et al., 1999; Steinert et al., 2003; Kovalenko, Belyi, and Bebeshko, 2003). An exception was a study investigating the prevalence and the characteristics of lens changes in a pediatric population (5–17 years of age) surrounding the Chernobyl area (Day, Gorin, and Eller, 1995). Of the 1787 subjects (996 exposed, 791 unexposed) in an extensive study, a small (3.6%), but significant, group of exposed children manifested PSC lens changes consistent with those observed in other exposed individuals, such as the atomic-bomb survivors. These observations were supported by Fedirko and Khilinska (1998), who found PSC lens changes in a study of 461 children.

The findings of the recent Ukrainian/American Chernobyl Ocular Study (Worgul, 2005) are currently being prepared for publication. Beginning 10 years after the accident, ophthalmic examinations were conducted in 6 cities located in 5 Ukrainian regions or oblasts. A total of 8607 liquidators, who had adequate dosimetry and epidemiological data and had no pre-existing incidental eye disease, have received two ophthalmologic examinations. The liquidators in the study averaged about 33 years of age at exposure time, and about 45 and 47 years at the time of two eye examinations. Using corrected gamma dose estimates, the individual beta dose values to the lens of the eye were estimated, and individual uncertainty distributions were simulated (Worgul, 2005).

There have been a number of other Ukrainian studies of Acute Radiation Sickness (ARS) survivors and liquidators, which reportedly have made estimates of relative risk by dose and found vascular pathology and deterioration of accommodative capability (Fedirko, 1999; Sergienko and Fedirko, 2002; Kovalenko et al., 2003). Cataract studies also have been conducted at the Medical Radiological Research Center of Russia (Ivanov et al., 2004a) and at the Republican Research Center of Radiation Medicine and Human Ecology of Belarus. The Belarusian results to date are mixed: while the liquidators have statistically greater numbers of cataracts than the general population, the evacuees and residents of contaminated areas have statistically fewer cataracts. This unexpected result is being subjected to investigation. Besides, dose estimates for Belarusian liquidators also need further clarification. Unfortunately, the Expert Group did not have access to this material and therefore could not assess or comment on the findings.

Expert assessment

Consensus

Studies available indicate an increased incidence of changes in the lens of the eye following radiation exposure. Continuing the studies should provide a clearer picture of any risk at low doses, allow further refinement of the dosimetry, and defining the temporal pattern of progression of early cataracts or pre-cataract lens changes. Knowing that the latency for radiation cataracts is inversely related to dose, continued follow-up will help to define the low dose risk more precisely and improve information on the influence of other exogenous factors.

The Chernobyl experience represents a fertile resource to establish rational and representative standards for radiation protection of the visual system and provide reasonably definitive assessment of cataract risk from protracted radiation exposure.

As mentioned in the earlier chapters of this report, there are significant issues with regard to the accuracy of external doses recorded in Registries for liquidators. Dosimetry relative to the lens of the eye, and, in particular, for beta radiation, poses significant additional obstacles. Refinements in dose estimates are needed in the future.

A focus of the Chernobyl eyes studies is a hypothesis that radiation cataract/opacifications detectable by an experienced examiner may occur at doses lower than previously thought. These studies do not appear to support the older classic literature on radiation cataracts, which concluded that a relatively high dose threshold (e.g. 2 Gy) must be exceeded for cataracts to appear after ionizing radiation exposure. A recent ophthalmological screening of the Japanese cohort (Minamoto et al., 2004), analysis of patients who had computerized tomography (CT) scans in the Beaver Dam Eye Study (Klein et al., 1993) and a U.S. National Aeronautics and Space Administration (NASA) study of cataracts in the astronaut corps (Cucinotta et al., 2002) are all consistent with the findings from Chernobyl eye studies showing that even relatively low doses (about 0.25 Gray) may be associated with excess lens opacities.

Gaps in Knowledge

As it is not clear that a high dose threshold exists for radiation cataract onset (i.e. low-grade cataracts), an effort to characterize the magnitude of excess risk per unit dose to the lens and the dose threshold level should be investigated. Continued follow-up, together with increased inter-study cooperation, is necessary to achieve this goal. There is also a need to obtain precise estimates of radiation doses to the lens, and to control for potential confounding factors.

Chernobyl studies and indirectly, the most recent atomic-bomb survivor study provide uncertainty as to whether or not cataract progression may have a radiation dose threshold. To this end, it is important to carefully document the severity of cataracts so that better estimates of risk for vision-impairing cataracts can be obtained.

Relative to the above, criteria need to be developed to allow one to predict the eventual severity of visual function loss from radiation exposure of the eye.

What are the effects of the Chernobyl experience on ocular tissues other than the lens? There currently exists considerable controversy regarding effects on ocular tissues even at moderate radiation doses (<5 Gy), particularly on endpoints such as retinopathy, including maculopathy, and vascular potency.

In some studies it is not clear whether or how beta radiation may have contributed to the development of cataracts in liquidators. There is some indication that, under certain conditions, the beta contribution to cataract development could even exceed that of the gamma component (Osanov et al., 1993)

Conclusions

The eye studies reported for children and liquidators suggest that posterior subcapsular (PSC) cataracts are associated with exposure to radiation from the Chernobyl accident. Data from the liquidator studies suggest that exposures to doses on the order of 250 mGy may also be cataractogenic.

Possibly related to the cataractogenecity of radiation is the finding of a dose dependent loss of accommodative function of the lens. Retinopathy (maculodystrophy) and vascular changes are also non-lens endpoints of interest.

Recommendations

Continued eye follow-up studies of the Chernobyl population, particularly the liquidators for whom reliable dosimetry exists, will allow greater predictive capability of the risk of radiation-induced cataract onset and will provide the data necessary to be able to assess the likelihood of resulting visual dysfunction.

All studies should provide careful evaluation and description of how the doses to the lens of the eye have been calculated and their possible biases and magnitude of uncertainty. Particular attention needs to be paid to the clinical expression of the cataract, especially to opacities in the PSC regions, as a potential indicator of radiogenic origin of the opacity.

For reasons noted above, continued follow-up for cataracts in those who have been already recruited into on-going studies is highly desirable. However, an ocular examination, as a part of general-population monitoring after radiation exposure from Chernobyl, is unwarranted and a wasteful use of resources. Because cataracts are a major aging disorder, they are generally self-diagnosed. Since patients are aware of their reduced vision, they visit an ophthalmologist. Typically, if asymptomatic cataractous changes are diagnosed during a routine eye exam, the physician records the fact, but no treatment is prescribed until sufficient severity is achieved for surgical intervention.

The only indication for specific monitoring for radiation cataract development is in radiation exposed workers. Radiological workers, with a history of working at the Chernobyl site in the early days of the accident, should be examined at least annually. If early lens changes (pre-cataractous) consistent with radiogenic damage appear, more frequent follow-up (2–3 times a year) is indicated, given the worker continues to be exposed. If subsequent exams identify a definitive PSC cataract, the individual should no longer be permitted to work in a radiation environment.

Careful assessment of ocular tissues other than the lens should be incorporated into all on-going Chernobyl eye studies. The possibility of low dose effects in the back of the eye (retina and choroids) deserves particular attention.

Cardiovascular Diseases

Background

High doses of radiation to the heart and blood vessels can cause a spectrum of cardiovascular complications. These include pericarditis, myocardial fibrosis, muscular dysfunction, abnormalities in heart valves, myocardial infarction, electric-conduction disturbances, and atherosclerosis. The diagnosis of these conditions is difficult and not standardized internationally. After radiation therapy, the risk of fatal cardiovascular disease increases with younger age at irradiation, longer follow-up, higher doses, and larger volumes exposed. Histologically, radiation-induced lesions in vessel walls are similar to those produced by atherosclerosis. Pathological changes in coronary arteries of irradiated hearts include endothelial cell loss, a loss of smooth muscle cells and fibrosis in media and adventitia.

Recent reports in the non-Chernobyl literature have clearly demonstrated the direct association of cardiovascular diseases and radiation therapy for Hodgkin's disease (Adams et al., 2004), breast cancer (Darby et al., 2003), and peptic ulcer (Carr et al., 2005) during a long-term follow-up period. Exposure to high doses of radiation (approximately 10 to 40 Gy fractionated doses) have also been reported to induce atherosclerotic lesions in cancer patients undergoing radiotherapy (Al-Mubarak et al., 2000). Experimental animal studies have shown that single doses of more than 5 Gy can accelerate the formation of atherosclerotic lesions. In contrast, studies of the survivors of atomic bombing in Japan, who received single doses to the whole body from 0 to 4 Gy, showed that cardiovascular disease risk was dose-related and increased by 14% per Gy (Wong et al., 1999). This evidence has been recently confirmed by the longer observation times in the Adult Health Study from 1958 to 1998 (Preston et al., 2003). According to this study, a significant positive and linear dose-response relationship has been confirmed for myocardial infarction among survivors exposed at less than 40 years of age (p=0.049). Concerning group studies of cause-of-death among atomic-bomb survivors from 1968 to 1997, an estimate of the ERR per Sv for heart disease was 0.17 (95% CI 0.08–0.26). This was statistically significant, but there was no indication of significant risks in any of the more detailed subgroups, because the number of cases analysed was small. The risk factors for cardiovascular disease, such as hypertension (Yamada et al., 2004) and hypercholesterolemia, were also increased in atomic-bomb survivors. The ERR value of 0.54 from the Chernobyl data in Russia tends to be higher than the value of 0.17 from the atomic-bomb data, but the 95% confidence intervals overlap.

While the changes after high doses are well characterized, those after low doses are less so and may include various aspects of oxidative stress associated with chronic exposures. Electron-microscopic studies of changes taking place during the latent stage of disease development indicated changes in endothelial cells of the myocardial capillaries with progressive obstruction of the lumen, resulting in formation of thrombi. Irradiation may cause fibrointimal hyperplasia, which leads to thrombus formation and potentially lipid deposition.

In the absence of radiation exposure, there are various factors that exacerbate the induction of cardiovascular diseases, such as hypertension and hypercholesterolemia. Besides direct factors there are other indirect influences on the initiation and progression of disease, such as lifestyle changes in physical activity, consumption of alcohol, and diet. Tobacco use is an often unappreciated, but very significant factor in the etiology of cardiovascular disease. It has been estimated that smoking accounts for as many, or more, cardiovascular deaths than lung cancer deaths.

It was reported in the UNSCEAR 2000 report that a number of studies have addressed the general morbidity of populations living in contaminated areas (UNSCEAR, 2000). The exposures were chronic external and internal irradiation from accumulated ^{137}Cs (essentially beta rays). When individuals in the contaminated areas were compared with the general population in these countries, increased morbidity due to diseases of the endocrine, haematopoietic, circulatory and digestive systems was found. A higher rate of mental disorders and disability had also been noted. It was difficult to interpret these results since the observations may have been, at least partly, explained by the active follow-up of the exposed populations and by the fact that age and sex were not taken into account in these studies. On the other hand, since the existing epidemiological studies of radiation-exposed populations were not consistent with these findings, they may have reflected a real increase in morbidity following the accident, which would mainly be an effect of psycho-social trauma, alcohol, smoking, and other factors. Stress and economic difficulties following the accident were most likely influencing the results. The pattern in causes of death in Ukraine was stable, with some decrease in cardiovascular mortality (WHO, 1995a).

On-going studies

Belarus

There are studies of mortality rates from coronary heart diseases in radiation contaminated areas (Grakovich, 2003; 2004), with total cohort size of near 1000 males. There is an indication of correlations between various traditional risk factors and mortality. However, at the time of the Expert Group Health meeting in September 2004, no information was available to the Group on national studies devoted to analysis of associations of radiation dose with disease prevalence and mortality.

Russia

In the cohort of 60,910 emergency workers, the long-term follow-up study of overall mortality demonstrated 4995 deaths. Of these, 1728 died of cardiovascular disease, which was much higher than the normal population rate (Ivanov et al., 2000). The estimate of the excess relative risk per Sv for deaths from cardiovascular disease was 0.54 (95% CI 0.18–0.91). The ERR/Sv for incidence of cardiovascular disease is less at 0.23 (95% CI -0.03–0.50) (Ivanov et al., 2004a). Of interest is that this latter value is driven primarily by hypertensive diagnoses, and it appears paradoxical that the incidence of ischemic heart disease and acute myocardial infarction (which might be expected to correlate with mortality) does not increase with dose.

Ukraine

Data on the prevalence of essential hypertension and coronary heart disease among all categories of Chernobyl victims in Ukraine have been reported (Khomazjuk et al., 2003). Sudden cardiac death was at the same frequency as death from leukaemia and lymphoma in survivors of the acute radiation syndrome (ARS) during 1987-2000, at two to three times the occurrence of other somatic diseases (Bebeshko et al. 2003). In 2001, the prevalence of cardiovascular diseases among clean-up workers was ranked highest among all somatic diseases. In the whole population, the incidence of cardiovascular diseases was ranked third (Buzunov et al., 2001a). A clinical-epidemiological investigation in 1992-2003 in Ukraine showed no clear evidence of an association of coronary heart disease with higher radiation doses (Buzunov et al., 2001b). The study of a cohort of 900 male clean-up workers demonstrated that coronary heart disease was associated with traditional risk factors for cardiovascular diseases such as age, tobacco smoking, hypertension and hypercholesterolemia. There is so far no clear evidence in Ukraine for an association of radiation dose and the prevalence of coronary heart disease.

Expert Assessment

Consensus

In Ukraine and Belarus there are no large epidemiological studies on the effect of radiation on the prevalence of cardiovascular disease. In Russia there is a large study of emergency workers that has shown a significant excess relative risk for death from cardiovascular disease in the exposed individuals. However, this result needs further evaluation at longer follow-up times and careful evaluation of competing causes. Also, further studies are needed for the general population, with a comparison of unexposed and exposed populations to different radiation doses and pattern of dose delivery. In addition, it is not clear why the incidence of outcomes that are expected to highly correlate with mortality (acute myocardial infarction and ischemic heart disease) are not correlated at all with radiation dose. Some of these discrepancies may be the result of comparison of the cohort at different time periods, non-uniform or inaccurate diagnoses or inaccuracies in registered causes of death.

Suggestions of a possible risk of cardiovascular disease per unit dose in liquidators must also be tempered by the known inaccuracies and limitations of the recorded doses in the Chernobyl State Registries.

The data from the Chernobyl accident so far, regarding the excess deaths from cardiovascular diseases in the emergency workers, are consistent with the published data from the atomic-bomb survivors.

Gaps in knowledge

The role of radiation in the induction of cardiovascular disease is not well understood, especially after chronic low doses.

The dosimetry estimates, particularly of liquidators, has known inaccuracies and these need to be improved.

Many of the cohorts do not have good non-exposed control groups.

The magnitude of possible inaccuracies of clinical diagnoses and causes of death is not known.

Some cohorts are small, so that statistical power is low.

Conclusions

Liquidators who recovered from the acute radiation syndrome and received high doses are likely to be at increased risk for cardiovascular disease.

There is a large study on Chernobyl emergency workers that has shown a significant excess relative risk per Sv for death from cardiovascular disease in the exposed individuals, but this has been found only in the Russian cohort, and there are some differences between incidence and mortality data. This result needs further evaluation and new studies designed to overcome the effects of bias and confounding factors (e.g. evaluation of the possible effect of dose overestimation). Further basic research and clinical epidemiology studies are needed to elaborate on these points.

The current data, while not fully substantiating an increase in cardiovascular disease due to radiation, cannot exclude a small effect that may be partially obscured by low statistical power or confounding factors.

Recommendations

Workers who recovered from acute radiation syndrome should be periodically examined for cardiovascular disease. The following would be scientifically helpful:

A study in animals to investigate the mechanisms of low-dose chronic radiation induction of heart disease should be undertaken, including the role of the immune and autonomic nervous systems.

A validation study should be performed in the three affected countries on the role of radiation in the induction of these diseases in emergency workers, using appropriate control groups, adequate dosimetry, common clinical and epidemiological strategies and standardized protocols.

Cytogenetic Markers: Their Use and Significance

Background

Even though there has, to date, been no epidemiological evidence of increased hereditary disease in the offspring of irradiated human populations, radiation effects on genetic material often generate serious public concern. Potential hereditary effects due to irradiation of gonadal tissues are covered more fully below in the section on reproductive effects. Genetic damage in somatic cells, however, implies increased risk of radiogenic cancer, for which there is abundant evidence. A number of tests currently exist that can show changes in genetic material of circulating lymphocytes at doses well below those that cause clinically apparent abnormalities. These tests are predominantly used as a biodosimeter in order to evaluate the magnitude of radiation dose to an individual. The existence of genetic alterations in peripheral lymphocytes carries no direct health concern to the individual. These are end cells that do not proliferate. However, as markers for radiation exposure, it is reasonable to infer that similar doses and, hence, genetic damage would have been received by other cells, most importantly stem cells, in the body.

Chromosome alterations in peripheral blood lymphocytes, in particular dicentrics but also micronuclei in binucleated cells and premature chromosome condensation (PCC) fragments, have been used as a biodosimeter immediately following a radiation accident. The limit of detection of these tests is approximately 200, 300 and 50 mGy, respectively for the above endpoints, if assessed soon after whole-body exposure (Darroudi et al., 1998). It is important to estimate an exposed individual's dose for several reasons. In the case of high exposures (> 1 Gy acute), information on dose assists in the planning of therapy and in alerting physicians to likely deterministic health consequences that could arise in the following weeks and years.

High doses of ionizing radiation clearly produce both early and late deleterious consequences in humans. At low doses (< 1 Gy), the situation is less clear, but the risks of induced stochastic diseases, notably cancers, are of great importance in relation to various issues, such as screening tests for cancer, occupational radiation exposure, manned space exploration and radiological terrorism. The hypothesis that chromosomal instability is the hallmark of a cancer even at the precursor cancer level carries considerable weight (Mitelman, 2000; Hagmar et al., 2001; Bezrookove et al., 2003).

While dicentric analysis of lymphocytes has been used for radiation dose assessment immediately following exposure (Lloyd et al., 1992), for historical exposures, difficulties in dose estimation exist due to the decrease in the number of cells containing unstable chromosome aberrations with time since exposure. The fluorescence *in situ* hybridization (FISH) technique, employing chromosome specific DNA libraries to "paint" individual human chromosomes, has opened new perspectives for rapid and precise detection of stable chromosome aberrations such as translocations. The inherent stability of translocations over cell generations has also enabled them to be used as a retrospective biodosimeter, thereby overcoming the temporal shortcomings of unstable aberration analysis. Evaluation of minisatellite mutations as a marker for prior radiation exposure has also been studied.

The primary purpose of this section is to examine the Chernobyl data to determine if there is good evidence directly linking chromosome aberrations or mutations to observed health effects.

Current status of evidence

The immediate medical response to the accident was the identification, assessment and treatment of those persons who received large radiation doses and suffered acute radiation syndrome. Dicentric cytogenetic biodosimetry proved to be the most quantitatively successful method for determining the patients' doses (Sevankaev and Zhloba , 1991).

Representative sampling of the large liquidator workforce showed elevated chromosome aberration levels that were generally consistent with average doses below about 250 mGy. Sevankaev et al (1995a), for example, examined almost 900 subjects using the dicentric assay and showed that, for the majority, the average doses agreed with average values in the Obninsk Registry. Certain specialist groups of recovery workers have been identified as having received considerably higher exposures. One notable group is some engineers and scientists who worked intermittently for several years inside the sarcophagus (Sevankaev et al., 1995b). Chromosomal studies, supported by some physical dosimetry, indicated protracted irradiations totalling several Gy.

Cytogenetic surveys of the general population in contaminated areas generally assumed lower priority and began later. Hence, use of the dicentric dosimetry required some allowance for the delay. Two such studies, starting about five years after the accident (Sevankaev et al., 1993; 1995c; Salomaa et al., 1997). They reported a number of children with rogue cells (cells with occasional metaphases and many aberrant chromosomes), while the remaining cells were essentially normal. The possibility of radioactive hot particles, or intense local dose rates from radioiodine in the thyroid, being responsible was discussed by the authors, but the most likely cause of these cells is viral and not radiological (Neel et al., 1992).

With the passing of time, as the dicentric assay became less meaningful, the emphasis on chromosomal studies has moved towards FISH. Salomaa et al (1997) took samples in 1993 in one of the last villages in Russia being evacuated, and estimated a mean dose of ~60 mGy. This is consistent with the dose of <100 mSv calculated from fallout parameters. During the 7 years, residents of those settlements had been subjected to various countermeasures to reduce their dose. Around the same time, another FISH study (Darroudi and Natarajan, 1996) was completed in four Belarus villages, and this indicated mean doses in the range 180–400 mGy. Finally 13–15 years post-accident, some Pripyat evacuees that had been originally assessed by dicentric analysis to have received 320 mGy were reassessed by FISH (Edwards et al., 2002). This method indicated ~200 mGy and, given the uncertainties, the findings of the two studies are compatible.

The mutation frequencies in repeated DNA sequences, termed "minisatellite loci" or "expanded simple tandem repeats" (ESTR), have also been examined. Some studies have suggested a relationship between mutation frequencies in ESTRs at low-dose irradiation from

Chernobyl (Dubrova et al., 1996; 1997; 2002), while others are equivocal or negative (Livshits et al., 2001; Kiuru et al., 2003). Overall, there appears to be no consistent pattern of dose response evident from the human data. Besides, the exact role of minisatellite mutations, which represent so-called "junk" DNA, in terms of health risk for future generations is not clear.

Dubrova et al. (2002) studied germline mutations at eight human minisatellite loci (i.e. repeat DNA sequences): CEB1, CEB15, CEB25, CEB36, MS1, MS31, MS32 (loci D2S90, D1S172, D10S180, D10S473, D1S7, D7S21, and D1S8), and B6.7 (located on chromosome 20ql3). These loci were chosen for their high spontaneous mutation rate in families from rural areas of the Kiev and Zhytomir regions of Ukraine, which were heavily contaminated by radionuclides after the Chernobyl accident. The control and exposed groups were composed of families with children conceived before and after the Chernobyl accident, respectively. The groups were matched by ethnicity, maternal age, parental occupation, and smoking habits, and they differed only slightly by paternal age. A statistically significant 1.6-fold increase in mutation rate was found in the germline of exposed fathers, whereas the maternal germline mutation rate in the exposed families was not elevated. These data, together with the results of previous analysis of the exposed families from Belarus (Dubrova et al., 1996; 1997), suggest that the elevated minisatellite mutation rate can be attributed to post-Chernobyl radioactive exposure.

Results of another international investigation dealing with 7 hyper variable minisatellite loci, CEB1 (D2S90), CEB15 (D1S172), CEB72 (D1S888), CEB42 (D8S358), CEB36 (D10S473), CEB25 (D10S180) and B6.7, revealed only a tendency to increased mutation rate without statistical significance. The authors concluded that the mutagenic influence of irradiation occurs only in the spermatogenesis cycle at the meiosis stage (Livshits et al., 2001). To test whether ionizing radiation can cause paternal genetic mutations that are transmitted to offspring, 88 families of Chernobyl clean-up workers exposed to ionizing radiation were studied (Slebos et al., 2004). Mutation rates using DNA blotting with the multi-locus minisatellite probes 33.6 and 33.15 and via PCR in a panel of six tetranucleotide repeats were analysed. The results indicated that children conceived before or after their father's exposure showed no statistically significant differences in mutation frequencies. An increase in germline microsatellite mutations after radiation exposure was found not to be statistically significant. No dependence of mutation rate on increasing exposure was found. A novel finding was that the tetranucleotide marker D7S1482 demonstrated germline hypermutability. Overall the data do not support an increased level of germline minisatellite mutations but suggest a modest increase in germline mutations in tetranucleotide repeats. Statistical power, however, was limited by the small sample size.

Most of the cytogenetic dosimetry studies were able to estimate the average doses to the bone marrow of an individual. These doses were cumulative lifetime doses excluding the normal level of natural background radiation, since this is taken into account through the age-dependent background rate of translocations. However, doses from unusually high background levels, contaminated areas, and doses received either occupationally or accidentally contribute to the excess yield.

Expert assessment

Consensus

Studies performed thus far for validating the FISH translocation technique revealed that it can develop into a reliable system for retrospective biological dosimetry at low doses (down to about 250 mGy). However, neither these data nor the minisatellite studies can be directly linked to induced DNA damage as a potential risk factor in human health at low doses, or to an increase in the frequency of a specific type of cancer.

Gaps in knowledge

Further studies are needed to evaluate the use of cytogenetic markers to estimate dose, including the development of unified scoring criteria, information on the background frequency (for stable translocations), application of multi-colour FISH for whole genome analysis, and the development of systems for automatic scoring of chromosomal exchanges. Few, if any, studies exist at present comparing cytogenetic markers and observable health effects in the same individuals.

Conclusions

To date, multiple tests of genetic changes in lymphocytes have been performed primarily to estimate absorbed doses to liquidators and persons resident in contaminated communities. Few, if any, of the studies have directly linked the findings with adverse health effects or outcomes. It is clear that the tests, as a marker of absorbed dose, can be used to provide a rough estimate of potential future risk in other tissues (e.g. the risk for radiogenic cancer). At present, this is a two-step process. Dicentrics or translocations indicate averaged whole-body dose. These values of dose may then be used to estimate risk using risk coefficients such as those proposed by international committees (ICRP, BEIR, UNSCEAR) and derived from epidemiological studies. In future, it may prove possible to develop a one-step process, and for this, the most promising biomarkers are clearly those that persist on a time scale of years. Stable chromosome translocations, as seen by FISH, are possible candidates, as they are the types of genomic changes associated with early steps to malignant neoplasms. Retrospective FISH studies on peripheral lymphocytes reflect transmissible lesions induced in the bone marrow stem cells and, therefore, may indicate the potential for haematological malignancies.

Recommendations

Further investigations are needed on radiation induced chromosomal aberrations, particularly in coordination with studies of biological dosimetry and epidemiology in the same population. Such studies should elucidate the potential role of induced chromosomal aberrations in adverse health effects.

Immunological Effects on Health

Background

The effects of ionizing radiation on the immune system have been reviewed in the past by UNSCEAR (1988). Impaired immunological function may be related to the risk of diseases and non-cancer mortality. This may occur as a result of radiation-induced depression or stimulation of the immune system.

The main function of the immune system is to protect the body against infections and probably some types of cancers. This occurs through a complex series of responses and defensive barriers. The majority of cells involved in the immune system response are leukocytes. There are innate and adaptive forms of immunity. Innate immunity includes the skin and mucous membranes, lysozymes, circulating factors (such as complements and interferons), pro-inflammatory cytokines (IL-1, IL-6 and TNF-α), phagocytic and natural killer (NK) cells. The adaptive immune response includes lymphocyte responses characterized by memory, specificity, diversity and self and non-self discrimination. Lymphocyte responses involve two distinct types of immunological reactions: the humoral (B-lymphocyte) and cell-mediated (T-lymphocyte) immunity. Humoral immunity is mediated by soluble antibodies that antigen-stimulated B-lymphocytes secrete with help from T-lymphocytes.

Decreased immune function has long been observed after high doses in radiotherapy patients. Prior studies of the atomic-bomb survivors exposed to more than 1.5 Gy have shown changes in cellular immunity (Awa, 1975; Akiyama, 1995; Kusunoki et al., 1998; 2002; Kusunoki, Yamaoka and Kasagi, 2002), particularly impaired responsiveness of T-cells and a reduction in the number of CD4 T cells. No change in natural killer cell numbers was identified (Keever et al., 1988; Bloom et al., 1988). In atomic-bomb survivors, there may be low-level inflammatory responses producing increases in C-reactive proteins and IL-6 (interleukin-6) (Hayashi et al., 2003). At very low (chronic) radiation dose rates, there is evidence of a chronic radiation syndrome affecting, in particular, the immune and neural systems. The threshold dose for depression of the immune system is about 0.3–0.5 Sv per year (Akleyev et al., 1999).

Prior Chernobyl studies relating to the immune system have yielded conflicting results. There was a report indicating a decrease in lymphocytes in recovery workers, however, this lasted only about a year (Kosianov and Morozov, 1991). Helicopter pilots who received higher doses did not show this effect (Ushakov, Davydov, and Soldatov, 1994), nor did Chelyabinsk recovery workers (Akleev and Kosenko, 1991). Studies of children were also conflicting. Children evacuated from Pripyat (Bebeshko et al., 1996) also did not have significant differences in immunological parameters from control groups. Children examined two years after the accident from Mogilev and Gomel did not show abnormalities in levels of T-lymphocytes, but showed a minor increase in B-lymphocytes (Galizkaya et al., 1990). UNSCEAR (2000) pointed out that 1) the levels of radiation that Chernobyl populations were exposed to had not been shown to affect the immune system in prior non-Chernobyl studies; 2) the findings of Chernobyl studies were not consistent with the known mechanisms and temporal effects of radiation on the immune system. UNSCEAR concluded that immunological effects in the general population could not be associated with Chernobyl and, when observed, were likely due to other causes.

Current status of evidence

More recent studies of emergency and clean-up workers have focused on levels and function of T cells and natural killer (NK) cells. Early studies reported a decrease in T cell counts and immunoglobulins (Chumak et al., 2001; Bebeshko et al., 2003; Vosianov, Bebeshko, and Bazyka, 2003). At 1–5 years post exposure there was variable recovery of cellular and humoral immunity. There were also variable responses of B cell counts. Thirteen years post exposure, none of the patients had developed classic autoimmune disease.

The results of more recent studies of clean-up workers have been controversial, and again, the results differ between studies. Many of the studies reported an initial decrease in CD3+ and CD4+ cells. Later reports showed an increase in these counts and a late decrease in CD8+ counts. Yarlin et al. (1993) reported a decrease in CD3+ cells in groups exposed to 0.1–0.5 Gy and another group exposed to 0.5–9 Gy, however there was a decrease in CD8+ cells only in the lower dose group and a decrease in CD8+ cells only in the higher dose group. In other studies of workers in the 30 km zone, Titova et al. (1996) reported a decrease in both CD4+

and CD8+ cells and Kurjane et al. (2001) reported that doses between 0.01Gy and 0.5 Gy reduced CD3+, CD4+ and CD8+ T-cells. Kuzmenok et al. (2003) did not find any changes in the levels these cell populations 11–14 years after the accident. The same study reported a possible increase in response of CD25+ cells to the cytokine interleukin-2, which was not proportional to dose. Kurjane et al. (2001) reported a decrease in NK cells, however these findings are in contrast to studies of the atomic-bomb survivors suggesting radioresistance. In addition, confounding factors exist. Some authors have reported a toxic effect of lead (which was dumped on the reactor) on CD4+ and CD16+ cells (Gridley, Pecaut, and Nelson, 2002). Also, elevated blood levels of lead, zinc and iron were found in Latvian and other clean-up workers (Kurjane et al., 2001; Nikolenko et al., 2002). Chumak et al. (2001) reported an accumulation of polyunsaturated fatty acids in peripheral mononuclear cells and esterified fatty acids in clean-up workers 11–14 years after exposure, as well as an increase in CD4+ cells and a decrease in CD8+ cells in heavily irradiated workers (also inconsistent with studies of the atomic-bomb survivors). Another study (Bazyka, Chumak, and Byelyaeva, 2003) of 730 emergency and 1212 recovery workers also reported decreases in CD3+ and CD4+ counts, but unexplained substantial, although smaller, decreases for the control groups.

The immune status of children around Chernobyl has also been studied. Titov et al. (1995) reported a variety of findings, including a decrease in B-cells and IgM (immunoglobulinM), but only for 30–45 days after the accident. A decrease in IgG was reported for 90 days, which later returned to normal and then increased. A study (Bebeshko et al., 1996) of 1118 children performed 5 years after the accident reported decreased CD3+ and CD4+ levels in children living in contaminated territories compared with children of the same age living in "clean" villages. This is in contrast to the study (Chernyshov et al., 1997) that showed lower levels of CD3+CD4+ cells in children with doses >1 mSv with respiratory disease compared to control children in uncontaminated areas. However, no decrease was seen in healthy children living in the contaminated zone. Koike et al. (1995) reported that children in Gomel had abnormalities in NK cell activity, but this was not correlated with the level of ^{137}Cs contamination. An *in vitro* study of lymphocytes by Padovani et al. (1995) suggested that there may be an adaptive response with increased radio-resistance after a preceding challenge dose of 1.5 Gy.

Autoimmune disease and thyroid disorders in children have also been studied (Vykhovanets et al., 1997). In many of these studies, the number of subjects is small, the method of study population selection is unclear, and absorbed doses were not estimated. Koike et al. (1995) studied children with goitre in contaminated areas and reported increased serum levels of IgG, IgM, IgE and a depressed level of NK cell activity. Other parameters were normal. Autoimmune thyroid disease and associated aspects are covered in more detail in Chapter 3.

Current studies in Ukraine at the Research Centre for Radiation Medicine (RCRM) include the role of cytomegalovirus and the possible abnormalities in early precursors of immunopoiesis as a long-term follow-up. A study of the immune status of children was recently finished by the Republican Research Center in Gomel and apparently does not reveal any significant abnormalities, although it has yet to be published in the international literature.

Expert Assessment

Consensus

Reported immunological effects of radiation exposure from the Chernobyl accident appear to be related mostly to changes in the amount or function of peripheral lymphocytes and serum immunoglobulin levels. These effects have been detectable up to the present time. Some of these effects may be due to confounding factors other than direct radiation such as stress, chronic infections, diet and chemicals. As a result, it is difficult to interpret the results. Immune effects would normally be expected to be significant in those workers who suffered from the acute radiation syndrome. Studies of children have shown varying results over time and between studies.

Gaps in knowledge

Current gaps in knowledge include the long-term effects of abnormal immune function after high doses of radiation combined with the effects of confounding factors, such as heavy metals on the immune system.

The role of signalling and regulatory pathways relative to data on lymphocyte counts and serum immunoglobulin levels is unclear in the exposed populations.

Conclusions

While effects on levels of immune cells and function have been reported in a number of studies, there is significant variation in the results of different Chernobyl studies, and some results are at variance with data from the atomic-bomb survivors. The possible role of confounding factors, such as heavy metals and the effect of radioiodine on the thyroid, also complicates the issue. To date, at doses of less than several tens of mSv, no clinical effects have been clearly related to abnormal immune function.

Recommendations

There should be continued study of immune effects after high absorbed doses, particularly in the survivors of the acute radiation syndrome. Studies of immune function in populations with less than several tens of mSv are unlikely to yield significant information.

Controlled studies of the incidence of both infectious and neoplastic diseases and a comparison of the immune system status in children from contaminated and clean areas may be of value. When these studies are performed, the individual absorbed doses should be evaluated, rather than simply stating the potential caesium or iodine exposure.

Reproductive Effects and Children's Health

Background

For purposes of this section, reproductive effects include fertility, potential hereditary effects caused as a result of parental exposure before conception, birth defects and infant mortality. An effort was also made to obtain information on the health of children at older ages. It is instructive to briefly review non-Chernobyl human studies regarding these effects and radiation exposure.

Fertility

The UNSCEAR review of the available literature indicates the following results: 1) temporary sterility of the testes occurs with single doses ranging from 1.5 to 4 Gy and with fractionated doses of 0.1 to 2 Gy, and 2) permanent sterility occurs with single doses ranging from 5 to 9.5 Gy and with fractionated doses of 2 to 6 Gy (UNSCEAR, 1982). Preconception irradiation of the male has been studied in a number of accidental exposure cases, including

Chernobyl. While doses of 1–6 Gy may cause either aspermia or hypospermia, a number of these individuals demonstrated "sterility" for several years, and then fathered normal children (Andrews et al., 1980). The ovary has temporary or reduced sterility with exposures of 1.5 to 6.5 Gy in a single dose and with 1.5 to 12 Gy in fractionated doses. Permanent sterility results from single doses of 3.2 to 10 Gy or higher fractionated ovarian doses.

Hereditary effects of preconception radiation

Several non-Chernobyl epidemiological studies have examined the effects of radiation exposure prior to conception. In 2001, UNSCEAR published an extensive review of the hereditary effects of radiation (UNSCEAR, 2001). It was concluded that no genetic (hereditary) diseases or effects had been demonstrated in human populations exposed to ionizing radiation. In spite of this, since ionizing radiation is a mutagen and genetic effects had been demonstrated in plants and animals, effects in humans were still considered possible. The dose that was considered to be responsible for doubling the normal incidence of spontaneous mutations (the doubling dose) was estimated to be about 1 Gy. Even high gonadal doses do not appear to have resulted in birth defects in the offspring. This is true after high doses (1–6 Gy), when radiation was used in an attempt to increase fertility (Kaplan, 1959; Lushbaugh and Ricks, 1972), after treatment for Hodgkin's disease (Horning et al., 1981), and even when radiation was administered to purposely cause sterility (Jacox, 1939).

In 1996, Cardis et al. estimated the potential hereditary effects in the Chernobyl population. The background risk of hereditary effects was estimated to be about 7.5 %. The excess due to radiation was estimated to be 0.03% in liquidators, 0.01% in evacuees from the 30 km zone, 0.03% in residents of the SCZs and <0.001% in residents of uncontaminated areas. These levels of potential effects are much too low to ever be statistically detectable. The 2001 UNSCEAR report revised downward risk factors of possible hereditary effects from prior levels, and thus current estimates of effects would be even lower. On the basis of these findings UNSCEAR (2001) concluded that no radiation induced birth defects, congenital malformations, had been demonstrated in humans.

UNSCEAR (2001) also discussed the possible genetic effects from the Chernobyl accident. Czeizel et al. (1991) reported that there was no increase in Down's syndrome in Hungary after the Chernobyl accident, however Sperling et al. (1994) reported a cluster of 12 cases in West Berlin (compared to 2–3 expected) nine months after the Chernobyl accident. Burkart et al. (1997) also reported an increase in Down's syndrome in Northern Bavaria. In both of the latter instances the radiation exposure was very low, and Burkart indicated that biological considerations argued against Chernobyl fallout as a plausible cause. DeWals et al. (1988) reported on chromosomal abnormalities, including Down's syndrome, in Europe and found no increase after May 1986.

Adverse reproductive outcomes following in utero exposure

Schull et al. (1981) examined the effect of parental exposure on other types of adverse reproductive outcomes in the survivors of the atomic bombings. Results were divided into the following categories: 1) untoward outcomes: the frequency of pregnancies that terminated in an infant who was grossly abnormal, was stillborn, or died within the first month of life; 2) survival of children; 3) sex ratio; and 4) cumulative experience of the children of parents who were exposed near the bomb detonation site. No statistically significant radiation effects following preconception irradiation were evident.

In 2003, ICRP reviewed the biological effects after prenatal irradiation of the embryo and fetus (ICRP, 2003). The main conclusions were that, during the pre-implantation period (0–10 days post conception), the lethality of the embryo is the dominating effect, and fetal/embryo doses of 0.5 Gy or less can cause pre-implantation death at certain radiosensitive stages. These data are from animal experiments, but there is no reason to believe that there are significant risks to health expressed after birth. In addition, during the pre-implantation period, the risk of induction of cancer and malformation is unlikely. The risk of malformation is greatest during the period of major organogenesis (3–7 weeks post-conception) with an estimated fetal dose threshold of around 0.1 Gy of low-LET radiation. It is then stated that at low doses the induction of malformations may therefore be discounted. The risk of reducing the intelligence quotient (IQ) after irradiation in the most sensitive period (8–15 weeks post-conception) is best described by a reduction coefficient of about 30 IQ points/Gy (for acute exposure). The threshold for severe mental retardation is about 0.3 Gy. For cancer induction as a result of *in utero* exposure, it is assumed that the nominal coefficient for risk of fatal cancer is, at most, a few times that for the population as a whole.

Lethal radiation effects in humans at late stages of pregnancy have been studied to a very limited extent. Harris examined 138 women irradiated with approximately 5 Gy of 200 kVp x rays at 6 to 18 weeks of pregnancy (Harris, 1932). This dose was sufficient to stop fetal growth in 2 weeks and to cause interruption of pregnancy in 129 of the 138 cases within 4 weeks. In a similar study, Mayer et al. (1936) indicated that a single exposure of 3.6 Gy caused abortion in a large majority of irradiated women. Some *in utero* lethal effects were demonstrated at Hiroshima and Nagasaki (Yamazaki, Wright, and Wright, 1954a; 1954b). Of 30 women who were pregnant and demonstrated signs of acute radiation syndromes, 7 (23 %) had fetal deaths, and 6 (20 %) had neonatal or infant deaths. In 68 women who were exposed at the same distance from the hypocenter, but demonstrated no signs of the acute radiation syndrome, fetal mortality was 10%. This was only slightly greater than the fetal mortality of the control group, which was 6%.

Little (1993) provided a comprehensive review of all the Chernobyl studies related to congenital abnormalities and adverse reproductive outcomes and pointed out that 1) the isolated reports of Down's syndrome were not confirmed in larger European studies, 2) no clear changes were apparent in congenital abnormalities in Ukraine and Belarus, 3) there was no consistent evidence of other measurable adverse outcomes of pregnancy (miscarriages, perinatal mortality, low birth weight, sex ratio shifts), 4) there was an increase in indirect effects such as abortions and lower birth rate related to anxiety, and 5) that there were no data on pregnancy outcomes relative to women who were pregnant at the time they were evacuated from the 30 km zone.

Current status of studies

Fertility

Even though the decline in fecundity in the three affected republics has been attributed to the effects of the Chernobyl disaster, no evidence exists that this is a dose related effect or one caused by a radiobiological mechanism. The Expert Group had no published or official information on this matter. Although, as will be discussed later in this text, the absorbed dose to the gonads of most adults are not sufficient to produce a decrease in fertility. An exception may be ARS survivors.

Birth rate

The birth rate in Ukraine has been declining, and currently there are less than 500,000 births per year compared to 800,000 in 1976. In comparison with the beginning of the 1990's, the total birth rate in Ukraine has declined by about 30%. The birth rate in the Chernobyl-affected populations is about the same as the average for Ukraine.

There has been a constant decrease from 12.1 live births per 1000 population in 1991 down to 7.8 per 1000 population at the beginning of 2001. The decrease in fertility among women appears to be the result of medical abortions requested as a result of maternal anxiety. In 2000, there were 113 cases of abortions per 100 live births and this index keeps increasing. The birth rate in the Western regions of Ukraine is 10.0–11.9 newborns per 1000 population, while in the eastern regions, such as Crimea and Kiev, it is about 6.1–6.5 children born per 1000 population (Bobylyova, 2001; EUROHIS, 2000). The expert group had no data on birth rate dynamics in Belarus or Russia.

Stillbirths and pregnancy and delivery complications

The stillbirth rate reportedly is decreasing in Ukraine as a whole, in the oblasts, and in both the contaminated and the control raions. Pregnancies with complications and birth defects have reportedly been on the rise. Birth defects are dealt with below. While the literature on these topics was provided to the expert group, it usually was of a descriptive nature and provided only percentage changes without specification of the time period or actual numbers involved. Thus, the Expert Group was not able to evaluate the evidence and draw conclusions.

Birth defects and Down's syndrome

There is an on-going study in Belarus by Lazjuk et.al. (1999; 2003) comparing pre- and post-Chernobyl accident data on rates of congenital malformation among abortuses and in newborns. The following congenital malformations were analysed: 1) anencephaly, 2) spina bifida, 3) cleft lip and/or palate, 4) polydactyly, 5) limb reduction defects, 6) oesophageal atresia/stenosis, 7) anal atresia/stenosis, 8) multiple congenital malformation group and 9) Down's syndrome. The results are shown in Figure 3. There has been a slow but steady increase in congenital malformations recorded in both high and low contamination areas, but the increase does not show a dose-response pattern. In the period 1983-1999, there were 12,167 congenital malformations registered among newborns and abortuses. In fact, there were statistically significantly less congenital abnormalities in the high contamination areas compared with low contamination areas, with a RR of 0.88 (95% CI 0.84–0.91).

There was also an increase in malformations registered from before the accident up until 1994, when the trend stabilized. The cause of the increase is not clear, but it does not appear to be directly attributable to radiation exposure. There also has been a retrospective study by the same authors of head circumference of *in utero* exposed newborns in Belarus, which appears to indicate smaller values in the exposed group. Again the reason for these findings is not clear, and the authors indicate the need for further study.

In Russia and in Ukraine, there is on-going state monitoring of reported congenital malformations, but there are only limited published data available, and the data are often contradictory. A study in Ukraine by Fedoryshyn et al. (2002) reported a statistically significant increase in congenital abnormalities in contaminated areas (Zhytomir) compared to a control area (Lvov), but as the authors mentioned, the value is "holding within the limits of spontaneous oscillations". When the data were confined to easily discernable and recognizable “model” abnormalities, there was no statistically significant difference (32.4 ± 17.9 per 10,000 newborns in the contaminated areas compared to 26.6 ± 7.2 in the control area).

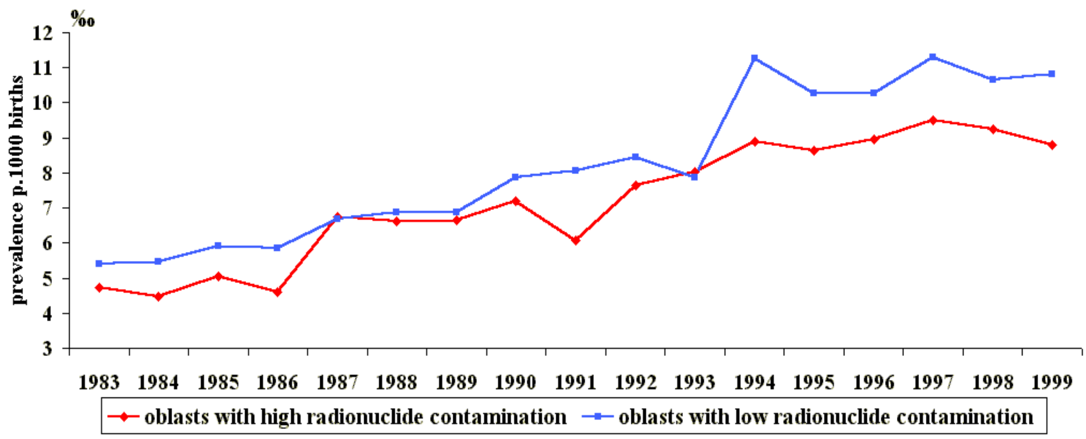

Figure 3. Prevalence at birth of 9 types of congenital malformations in 4 oblasts with high and low levels of radionuclide contamination (Lazjuk et al., 1999)

Information on birth defects and hereditary diseases among Chernobyl offspring is a part of the State Healthcare Statistical System under the Ministry of Health in Ukraine. In practice, an obstetrician or paediatrician completes registration forms in cases of congenital malformation or a hereditary disease/syndrome. Anomalies of extremities (such as polydactyly) are some of the most frequent findings in Chernobyl-affected children reported at the 3rd International Conference Fifteen Years after Chernobyl (Kiev, 2001). However, this information should be addressed with caution, as further analytical research will be needed to confirm such claims.

There is a report of an increase in Down’s syndrome in children conceived during the period of high radiation exposure in Belarus (Zatsepin et al., 2004) (Figure 4). The high value for the month of January 1987 is clearly seen in the figure. Overall, however there does not appear to be an overall trend in of an increasing incidence of Down’s syndrome from before or since the accident.

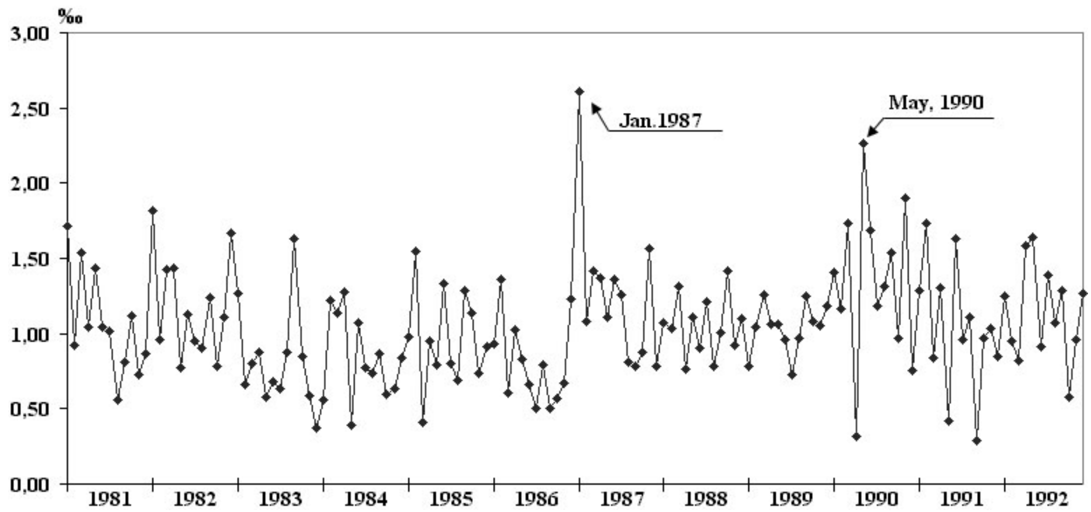

Figure 4 Monthly prevalence at birth of Down’s syndrome in Belarus for the period of 1981 to 1992 (n=1961) (Zatsepin et al., 2004).

Infant mortality. A number of terms are used to describe childhood mortality. Perinatal mortality is death during the first seven days of life, neonatal mortality is death during the first 27 days of life, and infant mortality is death during the first year of life. The infant mortality rate is the number of newborns dying under 1 year of age divided by the number of live births during the year and is reported per 1,000 live births.

The "Franco-German Initiative for Chernobyl" programme was conducted in 2000-2003 (Bebeshko, 2004). Its objective was to examine the changes in infant mortality in the contaminated Ukrainian oblasts of Zhytomir and Kiev and their most highly contaminated raions (5 each) compared to values in Poltava oblast, which was not contaminated. The study relied on official statistics. Dosimetry was reported in terms of both thyroid dose, collective dose and effective dose, although neither thyroid dose nor collective dose are relevant to studies of infant mortality. The average effective radiation doses for the inhabitants of these raions during the period from 1986 to 2000 varied from 6.0 mSv in the Polesskoe raion to 29.4 mSv in Luginy raion. The national statistics data are given in Figures 5-9.

The sets of bars in Figure 5 show that prior to the Chernobyl accident (1981-1985), infant mortality was higher before than after the accident in the Ukraine as a whole, in Kiev, in Zhytomir (contaminated oblasts) and in Poltava (a non-contaminated oblast). The last 2 sets of bars show that in the most contaminated raions, the infant mortality was much lower before the accident than in most other areas including the control raions. After the accident, infant mortality progressively decreased in both contaminated and non-contaminated oblasts. The only areas showing an increase (which is non-significant) were the most contaminated raions of the oblasts.

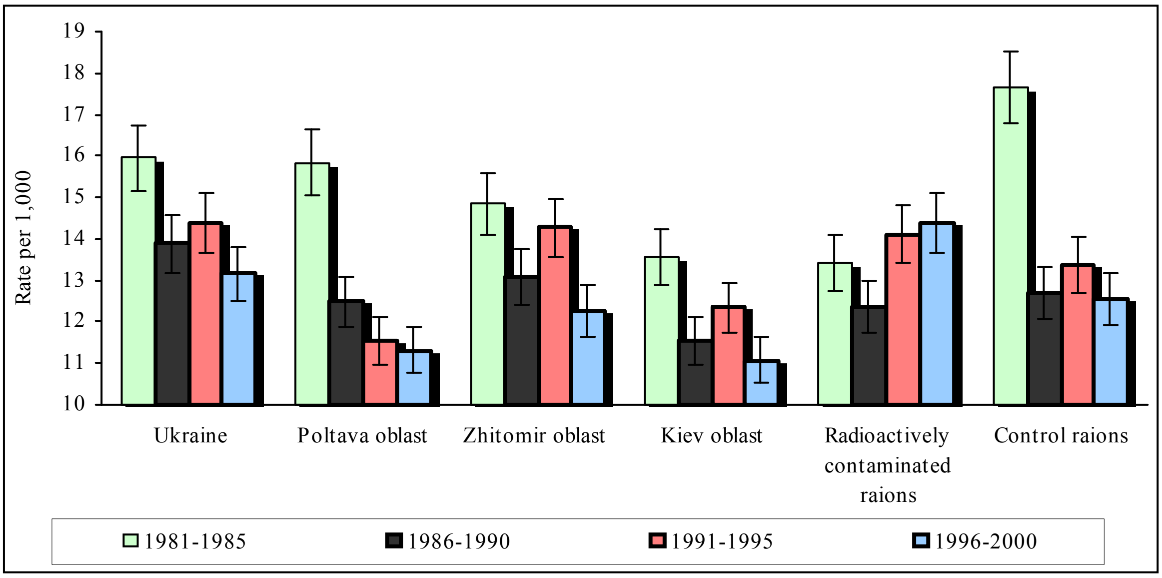

Figure 5. Infant mortality rates (95% CI) of Ukrainian population in different periods, per 1000 live born children.

Figure 6 shows much of the same information for the oblasts and Ukraine as a whole as was shown in Figure 3, however the data are given by individual year rather than multi-year periods. Again, the overall trend of a decline in infant mortality in Ukraine and oblasts is evident.

Figure 7 shows the infant mortality rate in the most contaminated raions of Kiev oblast by year before and after the accident. No clear trend is obvious, however there is major variation from year to year (possibly the result of small numbers). There are abnormally high outliers in the Polesskoe raion for the years 1996 and 2000 for unknown reasons.

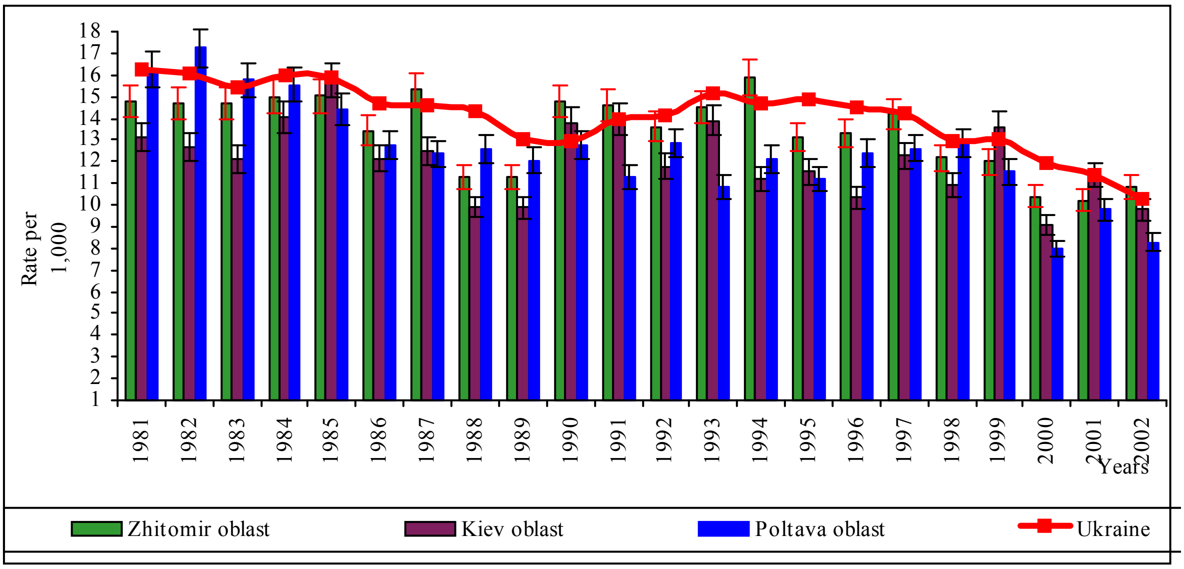

Figure 6. Dynamics of infant mortality (95% CI) in contaminated oblasts and in Ukraine as a whole, 1981-2002, per 1,000 live born children.

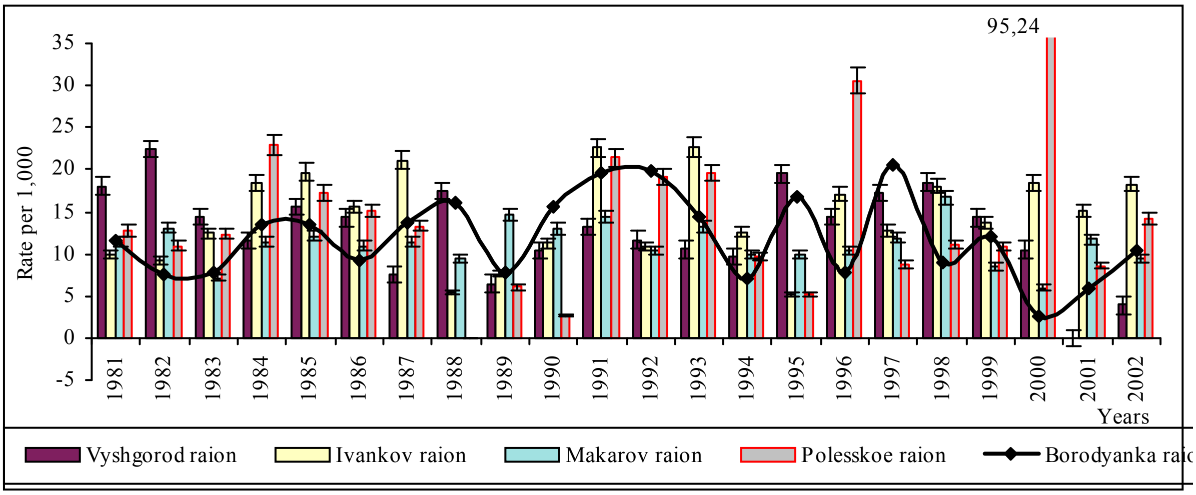

Figure 7. Dynamics of infant mortality (95% CI) in the most contaminated raions of the Kiev oblast, 1981-2003, per 1,000 live born children. Note should be made that the continuous line represents a separate contaminated region and not an average.

Figure 8 presents annual data for the 5 most contaminated raions in the Zhytomir oblast. Again no clear trend is obvious, however outliers are seen for the years 1987 and 2001 in the Narodichi raion. For reasons that are unclear, infant mortality is generally higher in Narodichi than other contaminated raions since the accident.

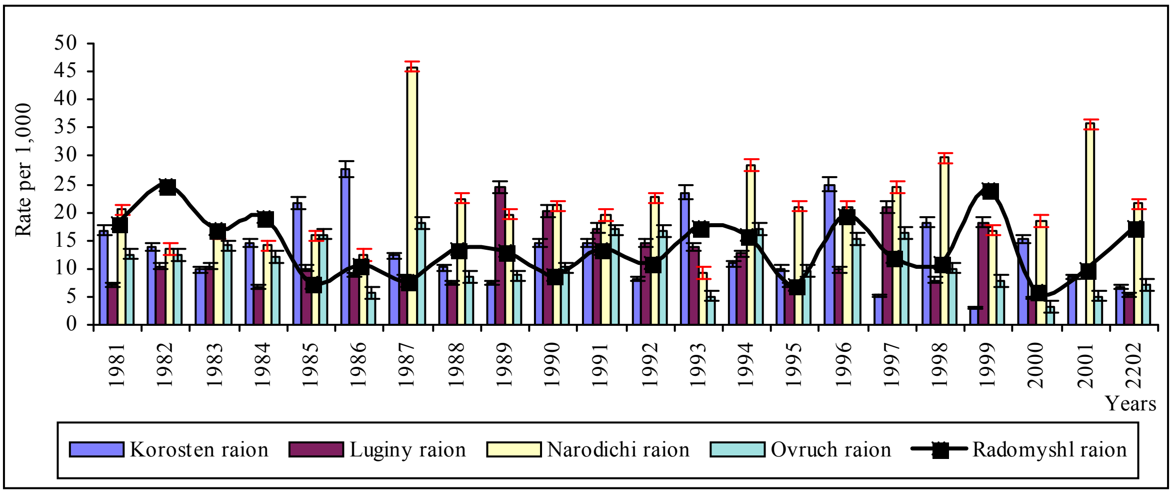

Figure 8. Dynamics of infant mortality (95% CI) in the most contaminated raions of the Zhytomir oblast, 1981-2002, per 1,000 live born children. The continuous line represents a separate contaminated region and not an average.

Figure 9 shows annual data on contaminated and control raions relative to infant mortality. There appears to be a slightly increasing trend over time in the contaminated raions and a slightly decreasing trend in infant mortality rate in the control raions. Inspection of the figure, however, shows that there were large differences between the contaminated and control raions in the years of 1981 and 1982, which drive these apparent trends. Of course, use of these data in years before the accident, when no contamination was present, is inappropriate, if one wishes to draw conclusions about radiation effects. If the data for the 15 years after the accident are used, the apparent trend of increasing infant mortality rate over time in contaminated raions disappears.

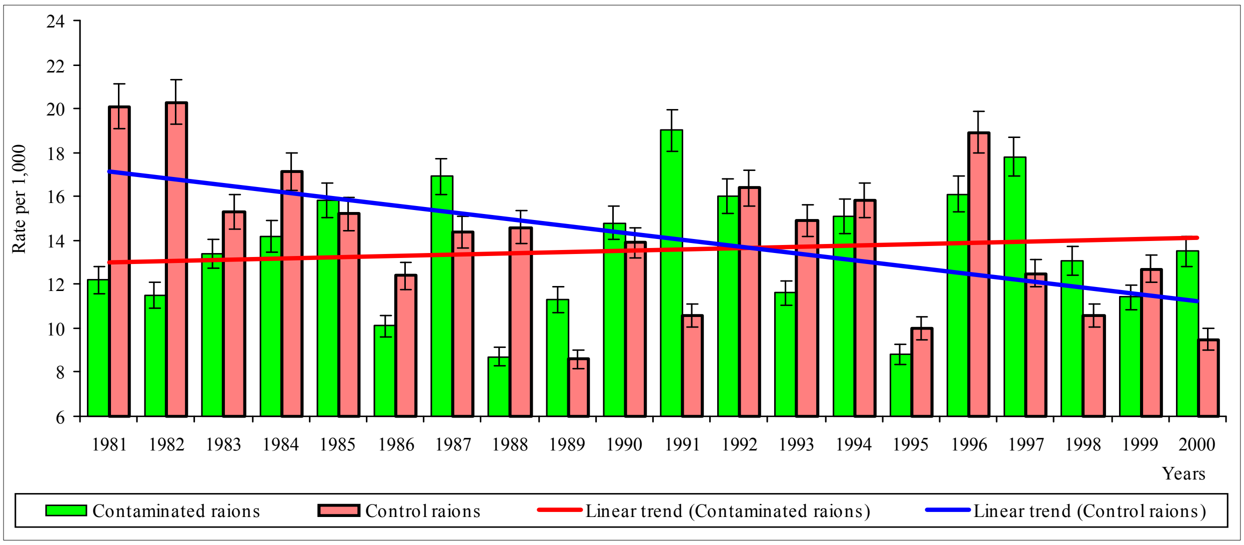

Figure 9. Dynamics of infant mortality (95% CI) in the radioactive contaminated and control raions in 1981-2000, per 1,000 live born children

Children's and adolescents' health

There have been many reports from Ukraine, Russia and Belarus stating that in children exposed to both Chernobyl related radiation and stress, health has deteriorated significantly. The literature on this topic was provided to the Expert Group. However, the material provided was usually descriptive and only gave percentage changes without specification of the time period, actual values involved and whether there was a relationship to absorbed radiation dose. Overall, no difference in mortality has been found between exposed and unexposed children in Ukrainian studies (Bobylyova, 2001).

A survey conducted in Ukraine revealed that some adolescents who were exposed as children to Chernobyl radiation apparently feel that they are doomed and therefore demonstrate reckless behaviour (e.g. engagement in criminal activities, prostitution, alcohol/drug addiction, and so forth). As a result, there has been institution of some reproductive health promotion programmes that include educational workshops by public health specialists and educational authorities. These provide Chernobyl adolescents with information on sexual hygiene, assist with psychological correction, social orientation, life planning skills, legal counselling, and individual and group support systems for pregnancy and parenting. (Buzunov et al., 2003).

On-going studies

There are a number of on-going studies of various aspects of non-cancer health effects among Chernobyl affected populations. The Expert Group did not have the opportunity to review all of these studies, however, some related to reproductive health are listed here. One study, conducted from 2004-2006 by the Institute of Hygiene and Medical Ecology of the Academy of Medical Sciences of Ukraine, is examining spontaneous abortion rates and congenital malformations. A study being conducted jointly by the Ukrainian Research Centre for Radiation Medicine and the Nagasaki University School of Medicine, Japan, is collecting data on dysmenorrhoea and menstrual syndromes (Korol and Omelianets, 2004).

Expert assessment

Consensus

The Expert Group has seen no evidence indicating that there is decreased fertility among males or females in the general population as a direct result of radiation exposure. Based on the scientific literature such effects would not be expected at the low dose levels of the general population.

Birth rates may be lower in contaminated areas because of concern about having children, and the issue is also clouded by the very high rate of medical abortions. The Expert Group did not have specific information on the fertility of the survivors of acute radiation syndrome.

No discernable increase in hereditary effects was expected based on the low induction rates estimated by UNSCEAR in 2001 and in previous reports of Chernobyl health effects. Since 2000, there has been no evidence provided to the Expert Group to change this conclusion.

While reported congenital malformations rose until about 1994, there is no evidence of a difference between low-level or high-level contaminated areas. This is consistent with other scientific literature indicating a likely threshold for congenital malformations at or above fetal dose levels of 100 mSv.

Infant mortality is much higher than in other countries, but has generally decreased in non-contaminated areas and less so in highly contaminated areas. This may be the result of different levels of medical care in the various zones.

Relative to the issues of stillbirth, pregnancy and delivery complication and the overall health of children, it has been extremely difficult to evaluate these from the material supplied to the Expert Group. As pointed out in some of the studies on mental and psychological effects in this report, there are likely reporting biases in much of the data related to general health of children. Also, data were supplied to the Expert Group without an indication of individual estimated doses. As a result, the Expert Group was unable to reach firm conclusions on these topics. Psychological issues of those exposed as children should be carefully considered.

Gaps in knowledge

The fundamental causes of the high level of infant mortality in both contaminated and control areas are unclear at this time.

While animal data exist on the lethal effects of radiation during the pre-implantation period, no human data are available.

No published information is available to assess the potential of any increased cancer risk as a result of *in utero* exposure.

Conclusions

Given the range of absorbed doses received by the vast majority of parents prior to or during conception, the Chernobyl epidemiological studies are consistent with evidence in previous scientific literature. They do not indicate a radiation related increase in malformations or infant mortality as a direct result of radiation exposure.

There has been a modest but steady increase of equal magnitude in reported congenital malformations in both contaminated and control areas since 1986. This does not appear to be radiation related and may be a result of increased observation or reporting.

The absorbed doses from the Chernobyl accident in adults, other than ARS survivors, are unlikely to have any effect on fertility.

The descriptive nature of information since 2000 provided to the Expert Group on stillbirths and adverse complications of pregnancy has prevented any conclusion regarding radiation effects. However, prior non-Chernobyl scientific literature at these dose levels would not support a radiation related effect. Further, we have not seen adequate scientific data clearly indicating an effect.

Infant mortality rates are high in both clean and contaminated areas. It is very high in a few selected areas. The reason for this is not clear. If data since the time of the accident is considered, there is no obvious temporal trend to indicate radiation as the direct cause of high infant mortality

While there is a reported significant decrease in the health of children, this has not been shown to be related to radiation dose and may be the result of increased anxiety, increased reporting, other non-radiation accident related causes or poorer health care. However, it was not possible to come to any firm conclusion on this issue. On the basis of other scientific literature, there is no reason to expect that the health of children will be affected as a result of parental radiation exposure.

Recommendations

In both contaminated and non-contaminated areas, the basic causes and actions to reduce infant mortality in all three affected countries should be vigorously pursued. The very high rate of mortality in selected areas, such as Narodichi, should be particularly examined.

Although, they are unlikely to provide useful scientific information on radiation effects, it is recommended that the local registers on reproductive health outcomes should be continued and improved as a public health measure.

Evaluation of long-term cancer risk in those exposed *in utero* would be valuable if reasonably accurate dosimetry can be obtained.

Actions to reduce the psycho-social impact of the accident on children and those who were children at the time of the accident should be taken (see also following section).

The population should be reassured that heritable effects and birth defects have not been shown to be increased by the accident.

General preventive health measures should be assessed and possibly increased for infants and children in both contaminated and non-contaminated areas.

Descriptive studies, which do not provide details of baseline values, time period studied, nature of the cohort, and do not evaluate dose-response relationships, should be discouraged. Controlled studies with appropriate controls and estimated individual doses that define and deal with confounding factors, have a blinded evaluation of subjects, and blinded analysis, should be encouraged.

Mental, Psychological and Central Nervous System Effects

Background

Four areas of concern in the field of mental health with relation to the accident, involve stress-related symptoms, effects on the developing brain, organic brain disorders, and suicide rate in clean-up workers. With respect to stress symptoms, increased levels of depression, anxiety (including post-traumatic stress symptoms), and medically unexplained physical symptoms have been found in Chernobyl-exposed populations compared to controls (Viinamaki et al., 1995; Havenaar et al., 1997a; Bromet et al., 2000). Studies have also found that exposed populations had anxiety symptom levels that were twice as high and were 3-4 times more likely to report multiple unexplained physical symptoms and subjective poor health (Havenaar et al., 1997b; Allen and Rumyantseva, 1995; Bromet et al., 2002).

Mostly these mental health consequences in the general population were subclinical and did not reach the level of criteria for a psychiatric disorder (Havenaar et al., 1997b). Nevertheless these subclinical symptoms had important consequences for health behaviour, specifically medical care utilization and adherence to safety advisories (Havenaar et al., 1997a; Allen and

Rumyantseva, 1995). To some extent, these symptoms were driven by the belief that their health was adversely affected by the disaster and the fact that they were diagnosed by a physician with a "Chernobyl-related health problem" (Bromet et al., 2002; Havenaar et al., 2003).

A great deal of concern has been expressed about the developing brain of those *in utero* when the accident occurred (Nyagu, Loganovsky, and Loganovskaja, 1998; Igumnov and Drozdovitch, 2000). On the one hand, the lowest level of exposure in which mental retardation was found in the offspring of survivors of the atomic-bombings was higher than the highest level of exposure reported for most Chernobyl populations. On the other hand, there is a general belief that the brains of Chernobyl exposed children have been damaged. Thus, the World Health Organization conducted the International Pilot Study of Brain Damage *In Utero*, but did not find that exposed children had elevated rates of mental retardation compared to controls (WHO, 1995b).

Consistent with the WHO report, two recent well designed studies using standard batteries of neuropsychological tests failed to find systematic differences in children exposed *in utero* (Litcher et al., 2000; Bar Joseph et al., 2004). Interestingly, in the Litcher et al. study (2000), 31% of the mothers of evacuee children believed that their child had memory problems compared to 7% of controls, even though there were no differences in neuropsychological test performance or school grades. This suggests that a perceived threat plays a powerful role in reports about health and mental health status.

Radiation effects on the brain have been documented in the non-Chernobyl literature after radiation therapy, in which fractionated doses above a total of 40 Gy were received. There has been little literature on radiation effects in adults with acute doses of 1–8 Gy, which was received by some of the liquidators. There have been numerous reports from Ukrainian and Russian researchers suggesting that the most highly exposed liquidators suffer from cognitive impairment, EEG changes, schizophrenia, dementia, signs of organic brain dysfunction (Loganovsky and Loganovskaja, 2000), and imaging changes on magnetic resonance (MRI) scans. Unfortunately, these findings have not been confirmed by independent investigators, and the biological basis of the relationship has not been demonstrated.

Rahu et al. (1997) reported that suicide was the leading cause of death among Estonian clean-up workers. Age-adjusted mortality rates from suicide were higher among the Chernobyl clean-up workers compared to the general population in Lithuania (Kesminiene, Kurtinaitis, and Rimdeika, 1997). The methods of registration of cause of death among the monitored group of clean-up workers in Lithuania differed substantially from those used in the general population, thereby making comparison with the general population problematic. However, in Estonia, the underlying cause of death was obtained from the death certificates at the Statistical Office of Estonia, and the rates were calculated in the same way as for the general population. These findings have not yet been replicated in studies of clean-up workers from other countries.

In general, the findings on the psychological consequences of the Chernobyl accident have been consistent with other exposure studies, such as research on the atomic bombings of Hiroshima and Nagasaki, the Three Mile Island accident, other neuro-toxic exposures in work environments, and other toxic environmental contaminations (Yamada, Kodama, and Wong, 1991). Nevertheless, the context in which the Chernobyl accident occurred makes the findings difficult to interpret, because of the complicated series of events unleashed by the accident, the multiple extreme stresses that occurred before and after the event, and the culture-specific ways of expressing distress. In addition, the affected population was officially given the label “Chernobyl victim” and frequently took on the role of "invalid" or disabled. It is well known that if a situation is perceived as real, it is real in its consequences. Thus, rather than perceiving themselves as “survivors,” the affected population perceived themselves as "victims" and not strong or having control over their future.

Current status of evidence

Population studies

A follow-up study funded by the United States National Institutes of Health (NIH), is currently underway to examine the physical and mental health of a cohort of 18–19 year olds, who were *in utero*–15 months old when the accident occurred and age 11 at the time of first assessment. The study addresses the extent to which initial perceptions of the event are risk factors for potential mental disorders, as well as the differences at age 18 between exposed children and their mothers versus the original classmate control group in Kiev and a new population-based control group from other unaffected urban areas in Ukraine.

Interventions

Pioneering efforts to address the mental health situation were launched under a Dutch humanitarian support project. In Gomel, a provincial capital in one of the most severely contaminated regions in Belarus, a health information center was organized. The center provides health information to the general public and, especially, to opinion leaders, such as doctors and teachers. It also offers psycho-social counselling to the population and organizes periodic health promotion campaigns (Nijenhuis et al., 1995). Another effort to address such problems was launched by the United Nations Education, Scientific and Cultural Organization (UNESCO). Working closely with local and national governmental and non-governmental organizations, nine Community Development Centers for Social and Psychological Rehabilitation were established across Ukraine, Belarus and Russia. The centers were located in places where large concentrations of evacuees or clean-up workers lived (Becker, 2002). The centers focus on community development and maintain various activities for different age groups, including individual and family counselling, support groups, day-care, play therapy and art therapy, a variety of workshops and classes, information services, and radiation and ecology education. Thousands of people have made use of the services provided by the centers since their opening in 1993-1994 (Becker, 2002). These programmes are only examples illustrating numerous local, regional, national, and international efforts being undertaken in the affected states in the field of mental health.

Expert Assessment

Consensus

The mental health impact of Chernobyl is the largest public health problem caused by the accident to date. The magnitude and scope of the disaster, the size of the affected population, and the long-term consequences make it, by far, the worst industrial disaster on record. Chernobyl unleashed a complex web of events and long-term difficulties, such as massive relocation, loss of economic stability, and long-term threats to health in current and, possibly, future generations, that resulted in an increased sense of anomie and diminished sense of physical and emotional balance. It may never be possible to disentangle the multiple Chernobyl stressors from those following in its wake, including the dissolution of the Soviet Union. However, the high levels of anxiety and medically unexplained physical symptoms continue to this day. The studies also reveal the importance of understanding the role of perceived threat to health in epidemiological studies of health effects.

Gaps in Research

There have been few studies integrating mental and physical health. The large cohort studies of cancer could provide a convenient opportunity to study these aspects of health conjointly.

There is a need for systematic research on highly exposed clean-up workers to confirm the Ukrainian and Russian reports about cognitive and psychiatric disorders and to extend knowledge about post-traumatic stress disorder, alcoholism and functional disability as a consequence of Chernobyl.

An adequately powered comprehensive, unbiased cohort study of children who were *in utero* or very young when the accident occurred is needed to evaluate their ability to function as young adults and to detect potential psycho-social and occupational impairment.

The evacuee population who were adolescents at the time are potentially at high risk for psychiatric, substance and psycho-social difficulties as a result of being uprooted at a vulnerable time in their lives and being stigmatized by their exposure experience. A comprehensive cohort study of this population to determine how this group coped with the stresses they faced has not been conducted.

Intervention studies are needed to examine the best approach to reducing the level of anxiety in this population. A WHO sponsored National Survey of Mental Health in a national sample of Ukraine found that people with mental health problems consult their primary care physicians, who lack special training in psychiatry.

Conclusions

The accident has had a serious impact on mental health and well-being in the general population. Importantly, however, it appears that this impact is demonstrable mainly at a sub-clinical level. Although the empirical studies do not support the view that the public anxiety bears a resemblance to clinical psychiatric disorders, such as phobia or psychosis, the disaster did have a psychological effect that is not limited to mental health outcomes. It also has ramifications for other areas of subjective health and health-related behaviour, especially reproductive health and medical service utilization, and the level of trust in authorities. Further, it may influence people’s willingness to adopt safety guidelines issued by the authorities.

What the Chernobyl disaster has clearly demonstrated is the central role of information and how it is communicated in the aftermath of radiation or toxicological incidents (Becker, 2004). Nuclear activities in Western countries have also tended to be shrouded in secrecy. The Chernobyl experience has raised the awareness among disaster planners and health authorities that the dissemination of timely and accurate information by trusted leaders is of the greatest importance.

Recommendations

In light of the complex nature of the stressors to which the population is exposed, and the high overall prevalence rates of psychiatric and substance disorders found in a recent WHO survey, it is recommended that a general public mental health policy be implemented, which is not limited to Chernobyl-related mental health problems.

Additional research on direct radiation effects on the brain in the most highly exposed liquidators is needed, with pathologic correlation if possible.

Every effort should be made to account for perceived threats to health in epidemiological studies of health effects.

The locus of care should move from the institution to primary health care settings (WHO, 2001), which provide a less socially stigmatizing and economically more efficient way of administering mental health services.

Significant increases in mental health training hours in the core training of physicians and nurses, as well as continuous and regular training programmes at the working place, are needed, especially for recognition and management of common mental health problems, alcoholism, and medically unexplained physical symptoms.

Renewed effort at risk communication, providing the public and key professionals with accurate information about the physical and mental health consequences of the disaster, should be undertaken.

Any new epidemiological or clinical research should be conducted collaboratively, in an open and transparent manner between researchers of different countries, and in relation to the population at risk.

Chapter 7

MORTALITY CAUSED BY RADIATION FROM THE ACCIDENT

Background

The question as to the number of deaths that are, or ultimately may be, attributable to the Chernobyl accident has been of great interest to scientists, politicians, the population at large and the mass media. Claims have been made that tens, and even hundreds of thousands of persons have died as a result of the accident. Given the two decades since the accident and the large number of liquidators and population who were or now reside in contaminated territories, it is clear that many thousands of persons have died from a diverse number of causes. The purpose of this chapter is to try to answer the question about the possible number of deaths attributable to radiation exposure from the Chernobyl accident.

To begin with, it is instructive to present some demographic information for Belarus, Russia and Ukraine for the year 2000 (Table 9). Data related to Poland are shown for comparison. After the break-up of the USSR in 1991, there was a substantial increase in the total population mortality rate and a markedly reduced average lifespan, particularly among males in the three countries for many reasons unrelated to the Chernobyl accident. Poland, with its similar geographical and historical conditions, has a lower death rate, much lower infant mortality rate and longer life expectancy than the other three countries. With rapidly increasing mortality in the three affected countries, it is extremely difficult to evaluate a contribution to this mortality caused by radiation exposure from the Chernobyl accident.

Table 9**.** Comparative population demographics for Belarus, Russia, Ukraine and Poland*.

Indicator	Belarus	Russia	Ukraine	Poland
Population (total), millions	10.3	147	49	39
Age 0-14	19%	18%	18%	19%
15-64	68%	69%	68%	69%
65+	13%	13%	14%	12%
Birth rate / 1000	9	9	9	10
Death rate / 1000	14	15	16	10
Infant mortality / 1000 live births	15	19	22	10
Life expectancy at birth	68	67	66	73
For males	62.6	58.4	66.7	70.6
For females	74.3	72.1	72.9	78.7

* U.S. Census Bureau International data base (www.census.gov/ipc/www/idbnew.html) and World Health Organization (www.who.int/countries), as of 2000.

The number of fatalities attributable to radiation exposure from the Chernobyl accident can be separated into the definite number of fatalities that occurred in 1986 due to acute radiation syndrome (ARS) in the emergency workers, as well as deaths in 1987-2004 among ARS survivors, and the much more indefinite number of fatalities that can be only roughly projected to occur above spontaneous mortality levels among both emergency clean-up workers and people living on contaminated areas in Belarus, Russia and Ukraine.

While the numbers of acute deaths due to ARS during the first months and year post accident are quite well known, the estimated numbers of subsequent deaths over the next 15 years that may be attributed to the accident has a moderate range of uncertainty. The estimates related to the number of deaths projected into the future are much less certain, as they are subject to other major confounding factors. These include competing causes of death and validity of the projection models for the particular circumstances of exposure. In reality, the actual number of deaths caused by this accident is unlikely ever to be precisely known.

Current Status of Evidence

Acute and sub-acute deaths

Information related to early deaths from the Chernobyl accident was published in the UNSCEAR 2000 report. A number of recovery workers and fireman received acute whole-body irradiation with high doses (i.e. 2 to 20 Gy) and died due to acute radiation sickness (ARS). These deaths occurred within the time period of one week to few months after exposure. Long-term sequelae may have led to the death of some ARS survivors during the subsequent years. ARS had been originally diagnosed in 237 emergency workers and later confirmed with detailed clinical analysis in 134 persons. Among these 134 emergency workers, 28 persons died in 1986 due to ARS, and 19 more died in 1987-2004 for different reasons. Among the general population affected by the Chernobyl radioactive fallout, the doses were very much lower than could have caused acute radiation sickness. There were thus no acute or sub-acute deaths caused by radiation in this group.

Studies of emergency workers

Fatalities due to the Chernobyl accident in workers with lower doses than those causing ARS symptoms have been estimated based on the data in the national registries of Belarus, Russia and Ukraine, which contain both dose and medical information for emergency workers.

Age-matched control and dose-response studies have been performed on the liquidators only in Russia. This is important because evaluation of the dose response is the most reliable method for revealing radiation induced health effects. However, even finding a dose response does not always guarantee that radiation was the direct cause of death, because of possible confounding factors, such as elevated rates of smoking or alcohol consumption, that may occur in persons who know they were exposed to radiation.

Among the 61,000 Russian emergency workers under study, 49,000 of whom were emergency workers in 1986-1987 and had individual external dose estimates, 4,995 deaths were recorded during 1991-1998. According to the data in the Russian National Medical-Dosimetry Registry (RNMDR), the standardized mortality ratios (SMR) for all causes of death (Figure 10) and for non-cancer mortality (Figure 11) of the 192,000 persons of the Russian emergency workers was lower, but did not significantly differ from the whole

Russian population (Ivanov et al., 2001b; 2004a). Until 2001, the standardized incidence ratio (SIR) (Figure 12), and until 1998, the standardized mortality ratios (SMR) (Figure 13) for all solid cancers in emergency workers did not differ significantly from the general Russian population. This is not particularly surprising, since in other radiation exposed populations, the excess risk of most solid cancers is not seen until after a latency period of 10 or more years post-exposure.

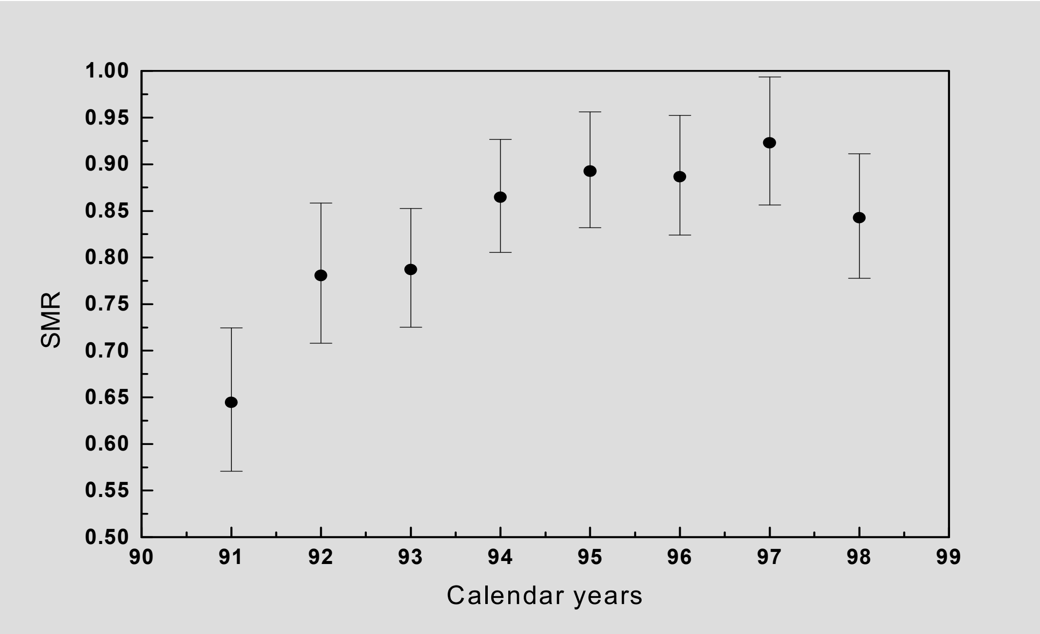

Figure 10. All causes of death standardized mortality ratios for Russian emergency workers compared to the general Russian population for the years 1991-1998 (Ivanov et al., 2001b; 2004a).

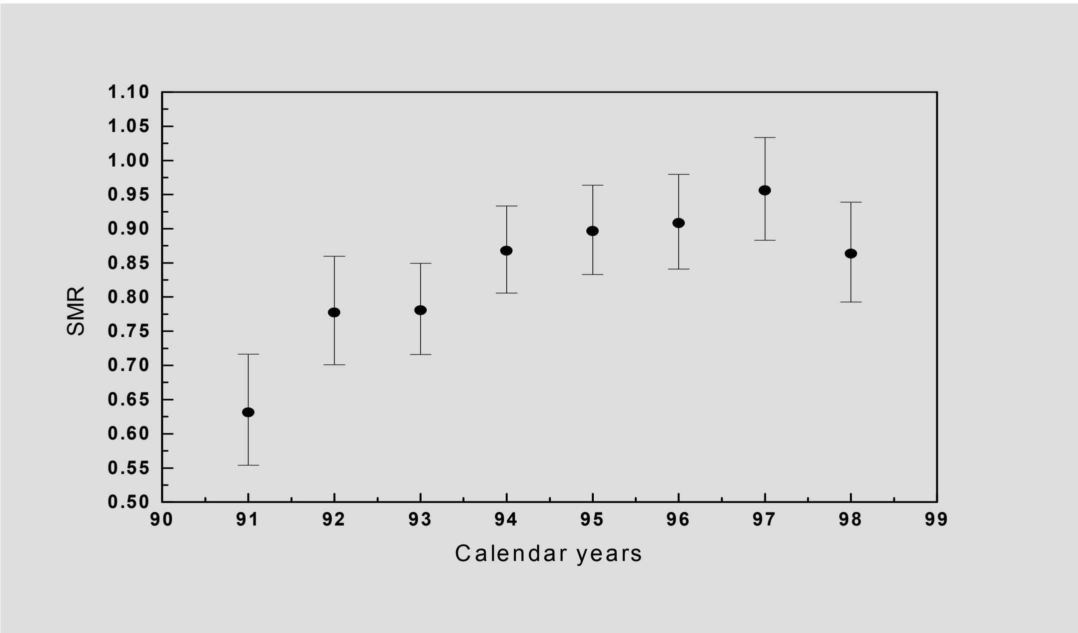

Figure 11. Non-cancer diseases standardized mortality ratio for Russian emergency workers compared to the general population for the years 1991-1998.

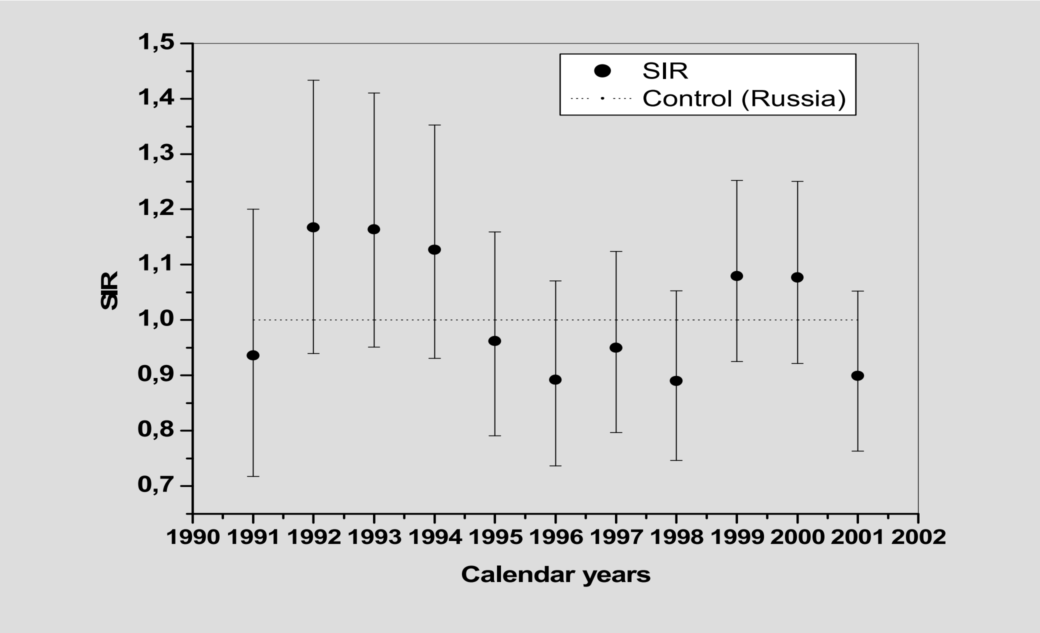

Figure 12. Solid cancer standardized incidence ratios for Russian emergency workers (data points with error bars) compared with the general Russian population (straight line) for the years 1990-2001.

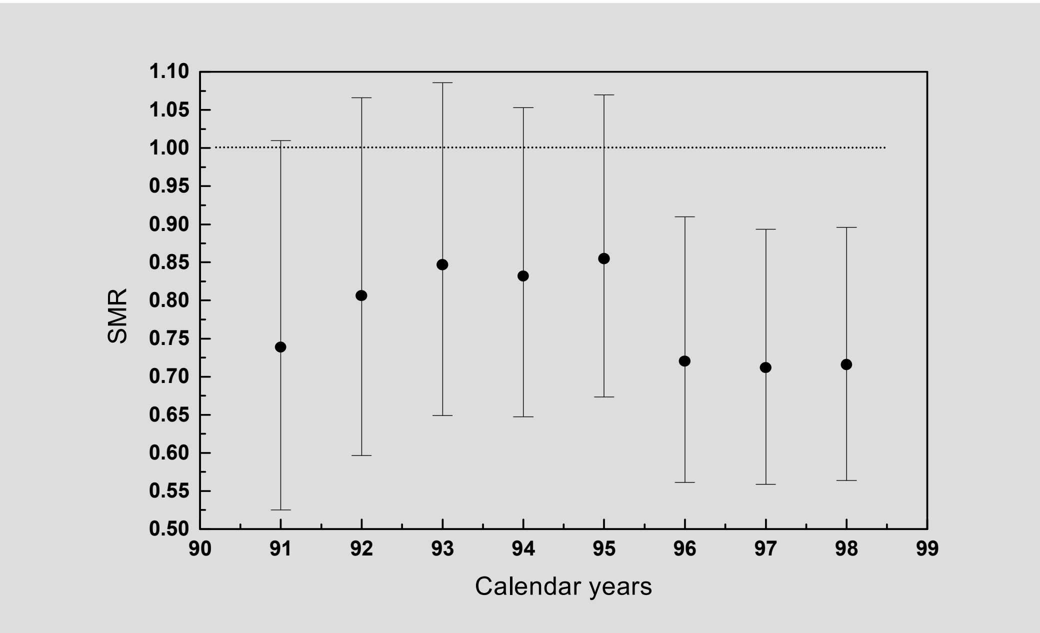

Figure 13. Solid cancer standardized mortality ratios for Russian emergency workers compared with the general population for the years 1991-1998

Recently there appears to be some increase in morbidity and mortality of Russian emergency workers caused by particular groups of diseases, such as leukaemia, solid cancer and possibly circulatory system diseases. The increase in mortality due to solid cancer has an excess relative risk per sievert (ERR/Sv) of 2.1 (95% confidence interval of 1.3 to 2.9). A similar increase has also been observed due to mortality from circulatory system diseases, for which the ERR/Sv was 0.5, with a wide 95% confidence interval of 0.2 to 0.9 (Ivanov et al., 2001a; 2001b; 2004a; 2004b).

Taking into account the average external dose of 107 mSv in the cohort under study and using the excess relative risks per unit dose, as described above, the number of deaths in Russian emergency workers attributable to radiation caused by solid neoplasms and circulatory system diseases can be estimated to be about 116 and 100 cases respectively (Table 10). This comprised 4.3% of all the deaths during 1991-1998 in the cohort under study.

In another study of the same group (Ivanov et al., 2001a; 2004c), in which there were 72,000 Russian emergency workers with individual external dose estimates, 58 leukaemia cases (ICD-9 categories 204-208) were observed during 1986-1998. Sixteen cases of chronic lymphocytic leukaemia were excluded from consideration, since, on the basis of many other studies, this leukaemia type is not thought to be caused by radiation. There was a statistically significant dose dependence of leukaemia deaths of ERR/Sv = 6.7 (95% confidence interval of 0.8 to 23.5).

Table 10. Number of deaths among Russian emergency worker cohort under study in 1991-1998 for main causes of death (Ivanov et al., 2001b; 2004b).

Causes of death	Malignant (solid) neoplasms	Non-cancer causes of death			Total
		Circulatory system diseases	Injuries and poisoning	Other	
All causes	515	1728	1858	894	4995
Attributable to radiation (mean and 95% range)	116 (72-161)	100 (33-168)	--	--	216 (105-329)

Once again, taking into account the average external dose of 107 mSv and excess relative risks per unit dose, the number of leukaemia cases attributable to radiation in this cohort can be estimated to be about 30 (42 × 6.7 Sv^{-1} × 0.107 Sv). According to more recent data (Ivanov et al., 2004c), mortality among leukaemia cases is about 80%, which allows one to estimate the number of leukaemia deaths attributable to radiation in the cohort to be approximately 24. This comprises 57% of all the death cases caused by leukaemia (CLL excluded) and about 0.3% of all the death cases in 1986-1998 in the cohort under study.

Hence, according to the RNMDR data, if the Russian emergency workers were exposed to an average external dose of 107 mSv, the 4.6% of all fatalities that occurred during 12 years after the Chernobyl accident can be attributed, either directly or indirectly, to radiation-induced diseases. Among them, about 2.3% of fatalities were caused by radiation-induced solid neoplasms, about 2.0% by circulatory system diseases and 0.3% by leukaemia. This assessment implicitly assumes that the risk of cancer is linearly proportional to dose, even at low levels.

Despite the statistically significant association between mortality from circulatory system diseases and radiation dose, the issue should be interpreted with special care. This is because of possible indirect influences of confounding factors, such as stress, unhealthy life style, and so forth. These estimates of deaths attributable to radiation exposure should be considered preliminary, and further peer review and continued studies are needed to provide more precise estimates. The issue of cardiovascular disease and its possible relationship to radiation exposure is treated in more detail in Chapter 6.

An estimate of the mortality rate attributable to Chernobyl radiation exposure can be obtained from the cohort of the Russian emergency workers described above and extrapolated to the rest of the Russian emergency workers (192,000 persons), assuming that the age, gender and dose distributions are similar in these groups. One could also use the Russian data to estimate mortality for the Belarusian and Ukrainian emergency workers (74,000 and 291,000 persons, respectively) assuming the same distributions occurred. Such estimates, however, have not yet been made.

So far the increased mortality in emergency workers has only been estimated up to 1998. It is well known from long-term epidemiological studies, such as those among atomic-bomb survivors, that radiation-associated morbidity and mortality increases should be expected during the decades to come. This is especially relevant for solid cancers, except for thyroid cancer, because the current observation period is only slightly longer than the recognized minimum latency period of about 10 years for many of the cancers. Since the risk of leukaemia decreases several decades after exposure, its contribution to radiation induced morbidity and mortality among Chernobyl emergency workers is likely to become less significant as time progresses. Because of the uncertainty in the epidemiological model parameters, any prediction for the future mortality based on recent RNMDR findings should be made with caution.

Studies of populations of the contaminated areas

At the present time, there is little peer-reviewed scientific evidence showing an increase above the spontaneous levels from cancer, leukaemia, or non-cancer mortality in populations of the areas affected by the Chernobyl fallout. Some information on total death rate of the population living in Ukrainian areas contaminated with radionuclides is presented in Table 11. Due to socio-economic reasons, the territories referred to as contaminated areas and their population size were administratively enlarged during 1986-1992.

With a total population in Ukraine of about 50 million and with a reported death rate of about 16.5 per 1000 persons annually, the expected number of deaths annually in Ukraine as a whole would be about 825,000. Thus, the deaths from all causes occurring among Chernobyl affected populations appear to be about 3-4% of all deaths in Ukraine for the 15 year period. It should not be interpreted that these deaths were due to radiation. Information in that regard can only come from analytical studies with age-matched control populations.

The annual death rate for those living in contaminated areas is about 18.5 per 1000, compared to 16.5 per 1000 reported for the rest of Ukraine. The reason for the difference is not clear, and without specific knowledge of the age and sex distributions of the two populations, no conclusion can be drawn. An apparent increase in infant mortality in contaminated areas is felt to be one possible cause. This is discussed in the Chapter 6 of this report. The Franco-German Initiative for Chernobyl has reported that the structure of the population living in contaminated regions of Ukraine includes fewer children and fewer young women than populations living elsewhere. There has been no concurrent increase in perinatal or early neonatal mortality. This also is discussed in more detail in the section on reproductive effects (Chapter 6).

Table 11. Number of persons and death rate for those living in contaminated areas of Ukraine (Korol and Omelianets, 2004).

Year	Total number of residents	Total number of deaths	Deaths/1000
1989	102340	1983	18.5
1990	109525	2271	20.7
1991	961179	14434	15.0
1992	1749694	30307	17.3
1993	1812862	33509	18.5
1994	1829341	32943	18.0
1995	1823084	33909	18.6
1996	1850508	34079	18.4
1997	1854671	33878	18.3
1998	1819858	32624	17.9
1999	1790995	32744	18.3
2000	1783092	33338	18.7
2001	1785090	32941	18.5

There have been many post Chernobyl studies of both morbidity and mortality caused by thyroid cancer, other solid cancers and leukaemia in the populations of areas contaminated with radionuclides in the three affected countries. To date, these have revealed only a statistically significant increase in thyroid cancer morbidity in children and adolescents. Thyroid cancer is discussed in detail in Chapter 3. Data from the heavily contaminated region of Bryansk on all solid cancers from 1980-1998 (Figure 14) do not show a clear increase over time compared to the incidence of solid cancers in the Russian population as a whole.

During 1992-2000, in Belarus, Russia and Ukraine, about 4000 cases of thyroid cancer were diagnosed in children and adolescents (0–18 years), of which about 3000 occurred in the age group of 0–14 years. For 1152 thyroid cancer patient cases diagnosed among Chernobyl children in Belarus during 1986-2002, the survival rate is 98.8%. Eight patients died due to progression of their thyroid cancer and 6 children died from other causes (Demidchik and Reiners, 2003). One patient with thyroid cancer died in Russia (Ivanov et al., 2004c). Taking into account that both excess relative risk of thyroid cancer in children and adolescents per unit dose (ERR/Gy) is > 10 and the fact that thyroid doses were high, one can estimate that a large proportion of the thyroid cancer fatalities can be attributed to radiation.

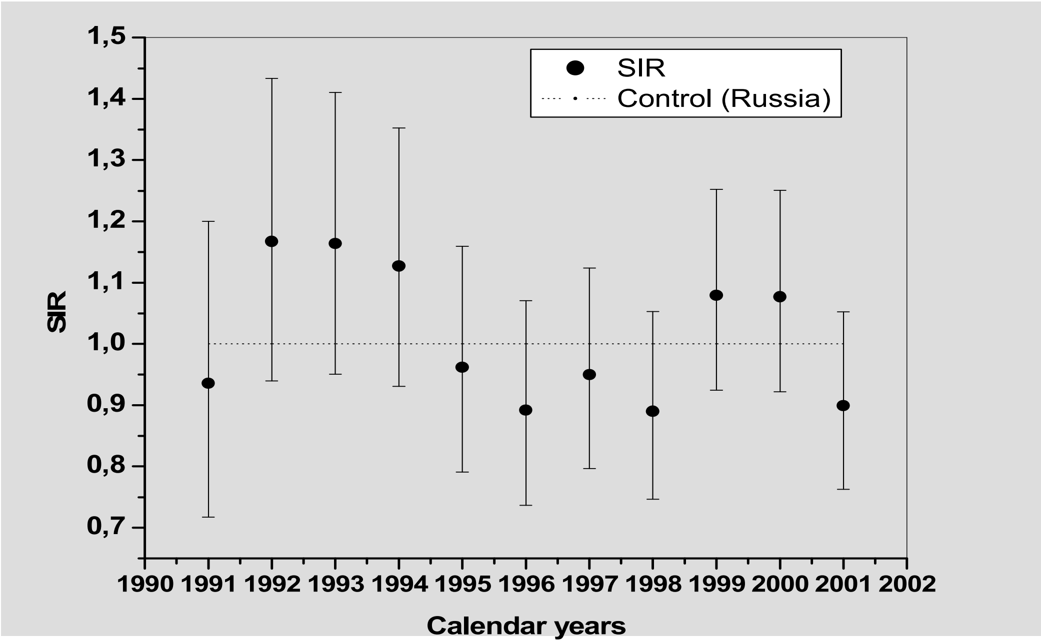

Figure 14. All solid cancer SIR among residents of 5 raions of the Bryansk oblast (both sexes).

Most likely, the main reasons for the lack of detection in the general population of a radiation related increase in cancer morbidity and mortality, except for thyroid cancer, are the relatively low absorbed doses and the high background incidence of cancer (except for leukaemia). For example, even for the area most contaminated with radioactive fallout after the accident, the Krasnogorsky raion of the Bryansk region in Russia, the average effective dose for adult inhabitants accumulated during 1986-2001 was about 50 mSv, although in some particularly contaminated villages of this district, the average accumulated doses exceeded 200 mSv (Bruk, 2002).

According to current radiation risk models (ICRP, 1991; UNSCEAR, 2000), this may cause a radiation related increase of total cancer morbidity and mortality above the spontaneous level by about 1–1.5% for the whole district and by about 4–6% in its most contaminated villages. Such an increase in overall cancer would be very difficult to detect with modern epidemiological methods. Cardis et al. (1996) presented an analysis of projected cancer deaths in the affected populations, using earlier estimates of population sizes. This assessment involved direct application of available risk factors, derived mainly from the atomic-bomb survivor study, without adjustments for the protracted dose rates or allowances for differing background cancer incidence rates and demographics in the Chernobyl exposed populations. Such estimates are thus intended to be order-of-magnitude or rough scoping estimates to be used for public health planning rather than as an accurate projection of actual cases. Cardis et al. (1996) concluded that for both solid cancers and leukaemia, the predicted proportions of excess deaths among all deaths from these diseases, or the attributable fractions, are small. For solid cancers, they range from less than 1% among the populations evacuated from the 30 km zone and the residents of “contaminated” areas outside the SCZs to about 5% for liquidators who worked in 1986 and 1987.

As shown in Table 12, the lifetime attributable fraction for leukaemia is greater than that for solid cancers in each population, ranging from 2–20%. The predicted lifetime excess cancer and leukaemia deaths for 200,000 liquidators, 135,000 evacuees from the 30 km zone, 270,000 residents of the SCZs were 2200 for liquidators, 160 for evacuees, and 1600 among residents of the SCZs. This total, about 4000 deaths projected over the lifetimes of the some 600,000 persons most affected by the accident, is a small proportion of the total cancer deaths from all causes that can be expected to occur in this population. It must be stressed that this estimate is bounded by large uncertainties, because of the only approximate applicability of the risk estimates and other factors, as mentioned above. The caveats mentioned in the conclusions of Chapter 5, on the risks of solid cancers in the Chernobyl situation bear repeating here.

For the further population of more than 6,000,000 persons in other contaminated areas, the projected number of deaths was about 5000 (Table 12). This latter estimate is particularly uncertain, as it is based on an average dose of just 7 mSv, which differs very little from natural background radiation levels. This would preclude any possibility of discerning these cases among the many more cases occurring for all different reasons. With the exception of thyroid cancer, direct radiation-epidemiological studies performed in Belarus, Russia and Ukraine since 1986 have not revealed any statistically significant increase in either cancer morbidity or mortality induced by radiation.

While no increase in overall solid cancer mortality has yet been detected, one must remember that with the known minimum latency of about 10 years and average latency about 20–25 years, the majority of radiation induced cancers would be predicted to occur in the future. Theoretically, leukaemia morbidity might be detected, if the population size was sufficient for statistical analysis of sufficient power. However, to date, no increase in leukaemia among the exposed general population has been found. The risk of leukaemia decreases about 10 years after exposure. Hence, the ability to detect leukaemia in the general population in the affected countries is less likely as time progresses.

Expert assessment

The recent morbidity and mortality studies of both emergency workers and populations of areas contaminated with radionuclides in Belarus, Russia and Ukraine do not contradict pre-Chernobyl scientific data and models. A mortality forecast based on pre-Chernobyl knowledge and available dosimetry data was made by Cardis et al. in 1996 for both the Chernobyl emergency workers and populations of contaminated areas. The attributable fraction of leukaemia mortality in emergency workers was predicted to be 79% for the first 10 years after the accident, which is in a good agreement with the observed 57% presented in this report. For the populations of contaminated areas the predicted lifetime attributable fraction of solid cancer mortality is about 3%. This is consistent with the lack of detection of a solid cancer mortality increase up to 2000.

Conclusions

Among the 134 emergency workers involved in the immediate mitigation of the Chernobyl accident, severely exposed workers and fireman during the first days, 28 persons died in 1986 due to ARS, and 19 more persons died in 1987-2004 from different causes. Among the general population affected by the Chernobyl radioactive fallout, the much lower exposures meant that ARS cases did not occur.

According to the RNMDR data, total mortality among Russian emergency workers does not differ in a statistically significant way from the age and gender standardized total mortality of the whole Russian population. However, increases in morbidity and mortality in emergency workers caused by leukaemia, solid cancers and circulatory system diseases were recently detected. Circulatory disease is discussed in more detail in Chapter 6.

The RNMDR data indicate that 4.6% of the Russian emergency workers fatalities that occurred during the 12 years following the Chernobyl accident can be attributed to radiation-induced diseases. Among them, about 2.3% of the fatalities may have been caused by radiation-induced solid neoplasms, about 2.0% from circulatory system diseases and 0.3% from leukaemia. All the data presented should be considered preliminary and in need of further peer review and continued investigation.

Epidemiological studies of residents of areas contaminated with radionuclides in Belarus, Russia and Ukraine performed since 1986, so far have not revealed any strong evidence for radiation-induced increase in general population mortality, and in particular, for fatalities caused by leukaemia, solid cancers (other than thyroid), and non-cancer diseases.

From more than 4000 thyroid cancers in children and adolescents (0–18 years) diagnosed in 1992-2002 in Belarus, Russia and Ukraine, less than 1% of patients have died from this disease, and the rest were treated successfully.

As elevated radiation-induced morbidity and mortality from solid cancers among both emergency workers and populations of contaminated areas might still be expected during the decades to come, this issue requires more research before firm conclusions could be made.

Because of the uncertainty of epidemiological model parameters, predictions of future mortality or morbidity based on the recent post-Chernobyl studies should be made with special caution. Significant non-radiation related reduction in the average lifespan in the three countries over the past 15 years remains a significant impediment to detecting any effect of radiation on both general and cancer morbidity and mortality.

Recommendations

Studies of liquidators and causes of their mortality should be encouraged, if individual dose assessment and the accuracy of such assessment can be determined. As mentioned earlier in this report, these issues may preclude useful epidemiological radiation studies of the liquidators.

Given the lack of statistical power based upon the estimated doses and confounding variables from causes other than radiation exposure, studies of the causes of mortality of the general population or evacuees from highly contaminated zones are unlikely to provide useful scientific information on radiation effects. However, they may have some value as a public health tool.

Table 12. Predictions of background and excess deaths from solid cancers and leukaemia in populations exposed as a result of the Chernobyl accident (Cardis et al., 1996).

Population	Population size/average dose	Cancer type	Period	Background number of cancer deaths		Predicted excess cancer deaths		
				Number	Percent	Number	Percent	AF[a] (%)
Liquidators, 1986-1987	200,000 100 mSv	Solid cancers	Lifetime (95 y)	41,500	21	2,000	1	5
		Leukaemia	Lifetime (95 y)	800	0.4	200	0.1	20
			First 10 years	40	0.02	150	0.08	79
Evacuees from 30 km zone	135,000 10 mSv	Solid cancers	Lifetime (95 y)	21,500	16	150	0.1	0.1
		Leukaemia	Lifetime (95 y)	500	0.3	10	0.01	2
			First 10 years	65	0.05	5	0.004	7
Residents of SCZs	270,000 50 mSv	Solid cancers	Lifetime (95 y)	43,500	16	1,500	0.5	3
		Leukaemia	Lifetime (95 y)	1,000	0.3	100	0.04	9
			First 10 years	130	0.05	60	0.02	32
Residents of other "contaminated" areas	6,800,000 7mSv	Solid cancers	Lifetime (95 y)	800,000	16	4,600	0.05	0.6
		Leukaemia	Lifetime (95 y)	24,000	0.03	370	0.01	1.5
			First 10 years	3,300	0.05	190	0.003	5.5

[a] AF: attributable fraction = (excess deaths/total death from the same cause) x 100

Chapter 8

PUBLIC HEALTH SYSTEMS IN THE CHERNOBYL REGION

General Considerations for Health Care and Medical Monitoring

Background

Health care after an accident is an issue of critical importance. The term "monitoring", when related to a radiation exposed population, has different meanings depending on the context in which it is used. In the early phase of a radiological event or accident there is a need to perform measurements with survey meters to detect the possibility of external or possible internal radioactive contamination of the persons involved. Such measurements should not preclude immediately instructing a possibly contaminated population to shower and change clothes and then return for radiation measurements and triage.

In addition to monitoring for contamination, there is a need to assess the population for potentially high absorbed dose levels as a result of external exposure and determining those with a need for emergency medical care. This is usually done by medically triaging those with symptoms of nausea, vomiting and/or diarrhea within the first hours or days post exposure. This type of initial monitoring and triage was done very effectively in the initial hours of the Chernobyl accident and undoubtedly saved many lives. Additional evaluation of potentially highly exposed persons can be made by serial evaluation of blood cell counts.

In the sub-acute or intermediate phase of an accident, the exposed population should have an initial medical evaluation. This is useful in order to place persons into various categories of needed medical care. Often, the majority of persons will have received very low doses and will not need subsequent medical care or follow-up. Such persons may be reassured that they have little risk. Placing them in a long-term medical follow-up programme often unnecessarily raises anxiety. Regardless of the level of dose, the persons should be supplied with accurate and appropriate information regarding their level and potential type of risk.

Those with low doses, but who are clearly very anxious, may need to be referred for counseling. These issues are discussed in detail in the section on mental health (Chapter 6). The initial medical examination may also identify potentially susceptible or sensitive subgroups that need additional consideration.

In the recovery or late phases of an accident there is the question of what long-term health care programmes are needed. One may expect that long-term medical follow-up over a period of years will be requested by virtually everyone who feels that they were exposed to radiation. Any programme to examine consequent health effects in a radiation exposed population should be carefully defined with regard to purpose and expected outcome. Long-term medical follow-up also means a number of different things to different people. For purposes of this report, there are three general categories considered:

- The first category of follow-up might best be termed "clinical care". For those persons who have received absorbed doses that have resulted (or may eventually result) in clinically significant deterministic effects (such as skin burns, cataracts etc.) should not only receive initial medical care, but also follow-up specifically targeting the organ system of interest.

- The second category of follow-up is best termed "medical monitoring" of the general population. That is, investigating for potential adverse events in hopes of changing their outcome. For most radiation-exposed populations, this is primarily directed towards neoplasms. A subcategory of medical monitoring is follow-up of potentially "sensitive subgroups" (e.g. children).
- The third category is follow-up for "epidemiological" purposes. That is, to relate effects to dose with the primarily purpose of scientific advancement and not for the direct benefit of the individuals involved.

Clinical care for patients with acute radiation syndrome

High doses of radiation may eventually result in long-term health effects. These include bowel obstruction, skin ulceration and thyroid hypo-function. Such outcomes will be specific to a given accident and to a given patient. The best approach is to relate the patients estimated organ doses to the organ effects and then to design an individual programme for follow-up and therapy. Persons requiring such programmes usually have had acute whole body doses in excess of 1 Gy or local doses in excess of 5 Gy. This report does not focus on the ARS medical management, as numerous publications are available on this matter.

Medical monitoring or screening

There then remains the issue of medical monitoring or follow-up in persons who have received lower doses (below 1 Gy). The term "medical monitoring" refers to the screening of asymptomatic populations in order to detect specific preclinical disease with the purpose of delaying or preventing the development of disease in those individuals

An exposure, or a presumed exposure, to radiation is not by itself sufficient to justify a medical monitoring programme (Guskova, Gusev, and Mettler, 2001; IOM, 1995; 1999). The decision about whether a medical monitoring programme is appropriate and necessary in a given situation should be based on consideration of a number of factors, including a rigorous cost-benefit analysis. This analysis should take into account the following characteristics: 1) the exposure of concern (e.g., its certainty, dose and temporal relationship of exposure to observation); 2) the disease of interest (e.g., its natural history and prevalence in the population); 3) the characteristics of available screening tests (e.g., their effectiveness, sensitivity and specificity); 4) the potential for the tests used to cause harm themselves; 5) the potential for action when test results are positive (e.g., the availability of and risks from follow-up evaluation); and 6) whether there is evidence that an intervention can improve the clinical outcome.

The justification for a proposed screening or monitoring programme can be assessed by considering the normal incidence rates and comparing these to the excess number of cases expected as a result of some exposure. If, for example, 1,000 people were exposed to a radiation dose that was estimated to increase the risk of developing cancer by one in a thousand, one additional case of cancer might occur compared to a spontaneous background of over 200 cases. Screening that entire population because of the one additional case would be unreasonable.

Those malignant diseases that have been epidemiologically associated with prior radiation exposure are termed *radiogenic*. With various degree of certainty, these include: leukaemia (all types except chronic lymphocytic leukaemia), cancer of the female breast, cancers of the lung, stomach, thyroid, esophagus, small intestine, colon, liver, skeleton, central nervous system, ovary, non-melanoma skin cancer, and cancer of the salivary glands. For some tumors (such as non-Hodgkin's lymphoma), whether there is an increased risk is not clear. For a number of cancers such as cervix, uterus, pancreas, multiple myeloma, and prostate, there is little evidence of increased risk associated with radiation exposure.

The latency period between radiation exposure and the development of a clinically detectable tumor will have an effect on the design of a screening programme. In the case of Chernobyl liquidators, most were between 20 and 40 years of age when they were exposed, and most radiation-induced tumors would be expected to become clinically evident when they are older than age 40, and in most cases, older than age 50.

Annual physical examinations

As early as 1922, the American Medical Association endorsed routine physical examinations for the general population in order to reveal current and prevent future illnesses (Dodson, 1925). This approach, along with the use of multiphase testing, yielded little new information and served to confirm already diagnosed illnesses. Therefore, in 1983, the American Medical Association issued a policy statement withdrawing its support for the standard adult physical examination (AMA, 1983). Canadian and Australian authorities have reached similar conclusions (Han, 1997). Annual physical examination of asymptomatic persons (both children and adults) by a physician is not currently recommended by WHO.

Cancer screening guidelines

As the primary health concern in an exposed population receiving less than 1.0 Gy is cancer, it is instructive to review current cancer screening recommendations. Recommended cancer screening tests change with time as randomized clinical trials are completed and as technology develops. One comprehensive source of current information and guidance is the report of the U.S. Preventive Services Task Force (1996). Most of the more than 50 screening interventions reviewed had insufficient evidence of effectiveness to warrant recommendation. Screening was only recommended for breast, colon and cervical cancer.

WHO also has recently published cancer screening guidelines for asymptomatic populations and indicated that "where the level of the incidence of cancer justifies it, and the necessary resources can be made available, screening for cancers of the breast and cervix is recommended". WHO also has stated that "screening for other cancer sites must be regarded as experimental and cannot be recommended at present as public health policy" (WHO, 2002).

Screening for radiogenic cancers in an exposed population

To date, for potentially radiogenic cancers, screening programmes have been shown to effectively reduce mortality only for cancers of the female breast and possibly colon. There is currently no evidence that annual blood examinations lead to earlier detection or reduced mortality from leukaemia, because the onset from laboratory findings to symptoms is rapid. At the present time, the effect of thyroid cancer screening in the Chernobyl population is not clear, and no guidelines currently exist in this regard. Screening for thyroid cancer is unique to those situations in which radioiodine is released and is not necessary in other types of accidents. Whether it is effective in reducing mortality or morbidity is currently unclear and probably should be done in appropriate populations until more evidence is accumulated.

Although the *Pap smear* for the early detection of cervical cancer has proven to be highly successful in reducing the rate of mortality due to this cancer among women, the cancer's association with exposure to radiation is equivocal at best. The *Pap smear* is, therefore, unlikely to be useful as a test in case of radiation exposure. The same may be said for prostate cancer screening tests.

Accuracy of monitoring and disease prevalence

False-positive and false-negative diagnosis of diseases can occur and must be considered when planning a monitoring programme. There may be serious medical consequences as a result of both false-positive and false-negative test results. One must address the psychological consequences of false-positive results. The prevalence of the disease of interest in the population has an effect on screening test accuracy. When a test is performed with a symptomatic population, the prevalence of the expected disease is reasonably high. However, in the screening of an asymptomatic population, the probability that the disease is actually present is low. As an example, if the test is being used for a population of 10,000 persons with a disease prevalence of 1 in 10,000 and the test has a 5 percent false-positive rate, there will be 501 positive results, of which one will represent true disease and 500 will be false-positive results (a positive predictive value of 1/501, or 0.2 %). The use of more than one test further reduces the positive predictive value. Even if the prevalence of disease in the screened population is higher (e.g., 1 %), the positive predictive value of a one-test screening programme rises only to 16 %.

Sensitive populations

There are situations when risk is low (and monitoring the general population is not warranted), but a monitoring programme might be justified for selected subgroups. Relative to radiation exposure, the predominant general factor that appears to affect radiation sensitivity to a number of cancers (such as thyroid) is age at the time of exposure. Sex is also related to the incidence of cancer following radiation exposure, as females have a slightly higher risk per unit dose than men. A particular group that may be included for special consideration are children of women who were pregnant at the time of exposure

There is the question as to whether genetic testing, or screening, may be helpful in order to assess risk following radiation exposure. At present, genetic testing/screening is not commonly used, and its ramifications are not clear (Wilfond et al., 1997). Genetic testing is mostly used in the clinical management of families with well defined inherited cancer syndromes and in certain cases in obstetrics. The 1996 American Society of Clinical Oncology (ASCO) Statement on Genetic Testing for Cancer Susceptibility set forth specific recommendations relating to clinical practice, research needs, educational opportunities, requirement for informed consent, indications for genetic testing, regulation of laboratories, and protection from discrimination (ASCO, 1996). It also addresses access to and reimbursement for cancer genetics services in the U.S. In updating this Statement in 2003, ASCO recommended that genetic testing be offered when: 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer (ASCO, 2003).

The issues of efficacy of intervention, test cost and accuracy, and disease prevalence considered throughout this chapter also apply to genetic testing in relation to the Chernobyl accident.

Assessment of the benefit of medical monitoring

Even with the availability of an accurate test, there must be a demonstration of the benefit of early detection. There must also be a lead time during which a tumor can be found as a result of monitoring before symptoms occur. If the patient presents with symptoms at the same time that the test becomes positive, then periodic testing will be of no benefit (e.g. leukaemia).

The availability of a sensitive and accurate test that detects a tumor before symptoms occur is still insufficient to justify the use of such a test in order to monitor the health of a population. There must also be an intervention or a therapy that is effective, available and acceptable to the patient. A number of screening programmes have found smaller tumors in high-risk populations (e.g., chest x rays of smokers), but the mortality rate was unchanged, probably because the tumor had already spread to distant sites in the body. As a result, even for smokers, who are at 5 to 10 times higher risk for lung cancer than nonsmokers, chest x rays are not recommended for monitoring or screening (Manser et al., 2003; Miller, 1985).

In order to justify a screening programme, randomized trials using the screening tests must show a benefit. The benefit can be measured in a number of ways. Commonly used parameters are the percentage of people who are cured and the percentage of fatalities that are averted. More difficult to measure, and therefore less desirable as study endpoints, are a decrease in years of life lost and an increase in quality of remaining life. Finally, effective use of a test depends on the clinician's sufficient understanding of the test, including knowledge of the appropriate interval for repeat tests, the cost and risks of the test.

Costs of medical monitoring

The International Agency for Research on Cancer (IARC, 1990) has pointed out that screening costs to be considered should include not only the financial cost of the initial medical actions but also the following:

- cost of intensive follow-up for false-positive results,
- emotional cost for false-positive results,
- cost of delayed diagnosis due to false-negative results,
- extension of period of morbidity for those in whom early detection does not improve survival,
- unpleasantness of screening test (e.g., colonoscopy)
- risk from screening (e.g., mammography).

An example of the major psychological costs associated with screening programs involves mammography. Mammography has rates of false positivity of 70 to 80 percent, so three of every four women who test positive must have a biopsy or surgery and suffer the accompanying physical risk and psychological fear before they learn that they do not have a malignancy.

Summary of medical monitoring considerations

A medical monitoring programme for asymptomatic persons exposed to radiation must take into account a wide variety of major factors before it is instituted. The major long-term effect that one might find after exposure to radiation doses below 1 Gy is cancer. Unfortunately, in any population, if the risk of cancer is high, few screening tests have been shown to be of benefit in terms of improving either survival or quality of life. Those that have been endorsed include the Pap smear and mammography.

One must also note that the incidence of radiation-induced cancer among those exposed to organ doses of less than 1.0 Gy would almost always be less than the spontaneous cancer incidence among non-exposed. If a monitoring or screening test is developed and an effective therapy is available, it is the higher spontaneous cancer risk, and not the radiogenic cancer risk, that should drive a decision to do monitoring. It is theoretically possible that a test may be developed that could assess radiation-induced genetic damage likely to lead to malignancy. If such a test were developed it could prove useful. None of the above should prevent symptomatic persons from receiving appropriate diagnostic tests.

Epidemiological follow-up

Epidemiological follow-up of a group of persons known, or presumed, to have been exposed to a potentially hazardous agent may be implemented in order to:

- identify adverse health effects in an *at-risk* group and to determine whether the risk of such effects is greater than that for a comparable non-exposed group of individuals,
- determine whether the increased risks that may be identified are associated statistically with the exposure,
- determine whether the increased observed risk is related to or influenced by other factors associated with or independent of the exposure, such as tobacco smoking and radon, and
- add to the scientific knowledge base, which can then be used to derive and refine risk estimates and to develop interventions.

Epidemiological follow-up studies may describe a disease situation in a defined group at a specific point in time (cross-sectional prevalence studies) or may collect information about group members over an extended time period (longitudinal studies). In prospective longitudinal studies, a defined population (or cohort) that has a common experience or exposure is followed forward in time in order to determine if there is an increased risk of disease among this cohort relative to that among a comparable, non-exposed cohort. Alternatively, groups of individuals with and without a specific disease, condition or cause of death can be compared retrospectively, using recorded data, in order to determine if the risk of exposure was greater in the diseased than in the non-diseased group.

The planning and implementation of epidemiological research involve many practical concerns, including:

- Availability of a clearly defined and appropriate study population with unique individual identifiers.
- Size and composition of the study population (as a general approximation, a population of 1,000 persons is needed to evaluate the carcinogenic effects of a dose of 1 Gy, 100,000 persons are needed to evaluate the effects of 0.1 Gy and 10,000,000 persons are needed to evaluate the effects of a 10 mGy dose).
- Completeness (and lack of bias) with which study subjects can be enrolled.
- Magnitude and distribution of exposure to the hazard being studied.
- Accuracy, including the unbiased collection of data and adherence to a defined time frame, with which the exposure can be measured (measurement of absorbed dose, as in the atomic-bomb survivors, is extremely important since the most compelling evidence of causality is the demonstration of a dose-response relationship).
- Disease identification (history of disease should be confirmed from hospital records, and causes of death should be determined by obtaining copies of death certificates).
- Background rate of a disease to be studied.
- Expected increase in the incidence of disease among the exposed group.

- Availability of information on other risk factors that might affect the outcome.
- Procedures to ensure valid consent for those research settings in which it is appropriate.

An epidemiological follow-up study typically begins by identifying two target populations: those exposed and those unexposed to the agent, treatment or characteristics being studied. It then seeks to determine whether the groups experience different health outcomes, during which the choice of an outcome or the measure of health affects study design, complexity, and feasibility.

Mortality is the outcome most conducive to an epidemiological study because the occurrence is clearly definable, happens at most once per person, and relatively complete records are available in many countries. Mortality is not, however, always the health outcome of interest. Many questions involve diseases and conditions that affect the quality of life but do not kill the individual. Physical and emotional health are often grouped under morbidity. Yet, concomitant employment, economic, and social well-being outcomes are increasingly being used as measures of effect. Finally, although not a direct measure of an individual's health, health care use and its cost to the individual and government agencies is a reasonable choice of outcome for some epidemiological follow-up studies. The study of death, illness, and cost poses substantial challenges to the epidemiologist.

Current Health Care for Affected Populations

Programmes specific for the various population groups

Current health care programmes in Belarus, Russia and Ukraine are different for survivors of the acute radiation syndrome, liquidators, populations living contaminated areas and the general public. A general description is provided here.

ARS survivors

Essentially all emergency workers who participated in clean-up operations during the first days after the accident obtained stable iodine in order to protect the thyroids. Acute radiation sickness (ARS) was initially suspected in 237 patients. These patients were treated in the Institute of Biophysics, Moscow, and in several hospitals in Kiev. Later, in 1989, the diagnosis of ARS was ultimately confirmed in 134 persons. However, all patients primarily diagnosed with ARS, regardless of diagnosis confirmation, are under long-term medical monitoring being carried out by the Institute of Biophysics (Russian Federation) and Research Center for Radiation Medicine (Ukraine). These two centers collect medical information concerning the health status of survivors after ARS (Bebeshko, 2004; Guskova et al., 2001).

Liquidators

Shortly after the Chernobyl accident, a system of specialized dispensaries for annual medical examinations of liquidators was established in the three affected states. At present, seven specialized dispensaries function in Russia, covering seven administrative territories across entire Russian Federation. In Ukraine, 13 specialized dispensaries provide monitoring of liquidators health status. In Belarus, until 2002, four specialized dispensaries carried out similar activities. Since 2002, this function was transferred to local health care systems based upon the liquidators place of residence. Overall coordination and methodological assistance is provided by the National Research Center for Radiation Medicine and Human Ecology in Gomel. Data on morbidity and mortality of liquidators in each state are collected in the following respective National Chernobyl Registries:

- National Research Center for Radiation Medicine and Human Ecology (Gomel), in cooperation with the Belarusian Center of Medical Technologies, Computer Systems, Economy and Management of Public Health (BelCMT, Minsk) in Belarus
- Medical Radiological Research Center (Obninsk) in Russia
- National Center of Information Technologies and National Registry of the Ministry of Public Health (Kiev) in Ukraine.

Liquidators may get urgent medical treatment in any hospital where they live. Specialized medical care in Russia is provided by several centers of the Ministry of Public Health, the Russian Academy of Medical Sciences, and the Ministry of Emergency. These Centres are located in Moscow, St. Petersburg, Obninsk, Rostov, and Yekaterinburg. In Ukraine, specialized health care for liquidators is provided by four institutions: Research Center for Radiation Medicine, Institute of Endocrinology, Institute of Urology and Institute of Neurosurgery in Kiev. In Belarus, medical care for liquidators is provided by regional medical preventive institutions, dispensaries, and national specialized centers. In addition to medical centers for regular examinations and treatment, there is a network of national rehabilitation centers and sanatoriums for liquidators in each of three affected states. Liquidators can receive rehabilitation treatment in these centers free of charge once a year as a part of their social privileges package.

Residents of contaminated territories

Shortly after the accident, the Ministries of Health of Belarus and Ukraine implemented preventive measures with respect to radioiodine and other radionuclides. On the morning of May 23, 1986, the Governmental Commission issued an official instruction to the Ministries of Health of Russia, Belarus and Ukraine on iodine preventive measures to be taken with respect to children living in rural areas with increased radioactivity levels.

In the three countries, networks of diagnostic centers have been established in the most contaminated regions. These centers provide regular medical examinations of the population. Financed by each government, medical care for residents of contaminated territories is provided by a three-fold system: raion, oblast, and state level. Usually, more complex diseases requiring more sophisticated diagnosis and treatment are handled by large national clinical and research centers.

Children living in contaminated territories or born to parents exposed to radiation

In Russia and Ukraine, all members of this group are regularly examined in dispensaries and out-patient clinics at raion and oblast levels. The treatment is provided at children's hospitals located near a place of residency. In Russia, results of examinations and treatment at the local level are sent to the Clinical and Research Children Centre for Radiation Protection of the Moscow Research Institute of Pediatrics and Children’s surgery. This Centre was established in 1991 and includes four branches situated in children's hospitals in St. Petersburg, Yekaterinburg, Rostov and Barnaul. The Centre and its branches provide specialized medical care for children. Childhood thyroid cancers are treated at the Research Oncological Centre in Moscow and Medical Radiological Research Centre in Obninsk. The Clinical and Research Children Centre in Moscow has established the All-Russian Chernobyl Children Registry, which includes information on children affected by the Chernobyl accident and children born to exposed parents. The health care system for Chernobyl children also includes 13 rehabilitation centres. They are functioning on the basis of children’s sanatoriums located in clean territories of Russia.

In Ukraine, the results of child health monitoring are collected at the National Registry of Ukraine, the Ministry of Health and at special sub-registries on hematology, endocrinology, and pediatrics at respective research institutes in Kiev. For child health rehabilitation, there are various centers and sanatoriums providing treatment free of charge.

In Belarus, all Chernobyl-affected children undergo annual medical examination and treatment, if necessary, at local childrens clinics and hospitals. The health status information is collected at the National Chernobyl Registry. In all three countries there are mobile teams of highly qualified medical specialists employed to assist local health-care providers at remote locations.

Scope of existing regular medical examination programmes

In accordance with State regulatory orders in the three countries, regular medical examinations are mandatory for all groups of the affected populations. These orders do not cover populations living in clean areas. The composition of the team providing annual medical examinations for target population varies from state to state and includes the following specialists: internist, neurologist, endocrinologist, oncologist, hematologist, ENT, gynecologist, ophthalmologist, and pediatrician.

Ultrasound examinations and whole-body-counter dosimetry may also be included. Laboratory examinations include routine investigations of blood, urine and general biochemical analysis. Thyroid hormones are also investigated, if needed. In Belarus, the routine examinations also include number of thrombocytes, dosimetry control, thyroid ultrasound and electrocardiograms. For individuals with high radiation risk, specific tests of biological dosimetry (i.e. cytogenetic tests and EPR dosimetry for tooth samples) are obtained.

Psychological support

Community centres for social and psychological rehabilitation of the affected population have been created in Ukraine, Russia and Belarus. Within the framework of the UNESCO-Chernobyl Programme, there are three centres in Ukraine, four centres in Russia and four centres in Belarus. These centres are functioning in settlements that have been affected in various ways by the accident. The community centres deal with the wide scope of psychosocial problems caused by Chernobyl. Objectives assigned to the community centres for psychosocial rehabilitation are: 1) improving mental health of all age and social groups in the community; 2) encouraging interactions within the community; 3) empowering community members to take control over their lives; 4) developing social responsibility; 5) promoting problem-solving skills.

The community centres promote positive development in the communities, which, in turn, positively affects an individual's mental health. The Community Centres network has developed psycho-social assistance models that are relevant to the post-accident period (intensified by social and economic crisis) that might also be applied to various types of crises (Korol and Omelianets, 2004).

The Ukrainian Association of Environmental Medicine has developed a programme for identifying behavior among adolescents that place them at risk for reproductive health disorders (i.e. early onset of sexual intercourse often resulting in unwanted pregnancy, alcohol abuse or drug consumption, and socially unstable family). It develops and shares media, oriented towards the Chernobyl adolescents, about sexual hygiene, psychological support and correction, social orientation, life planning skills, and legal counseling possibilities. It also provides individual and group support systems for pregnant and parenting Chernobyl adolescents, and adolescents with substance abuse and other psycho-social issues (e.g. alcohol- and drug addiction, unprotected promiscuous sex, gambling, etc.) (Korol and Omelianets, 2004).

Chernobyl invalids

It is recognized that the issue of classifying persons as Chernobyl "invalids", or disabled, is closely related to national social systems and regulations of the each affected state. Thus, an international body of experts is not in a position to issue guidelines and regulations on disability criteria. However, the question of disability is related to health and is still considered within this report to a certain extent. The term "invalid" and its use has also been discussed in the mental health section of this report (Chapter 6).

According to national regulations of Ukraine, to be classified as a Chernobyl invalid in one of the affected states, a person must meet all of the following criteria (Bebehsko 2004; Korol 2004):

- to belong to one of the Chernobyl populations (to have residence and/or work record).
- to be diagnosed with a disease included in the "official" list of diseases, disorders and syndromes considered by national public health authorities to be associated with the impact of Chernobyl.
- to have a loss of work-capacity (50% and greater).

There is some evidence from Belarus, Russia and Ukraine of the manipulation of diagnoses allowing persons to be recognized as a Chernobyl invalid without proper justification in order to obtain social benefits. To avoid such incidents, special expert commissions have been established in the three countries. These Commissions have established standard lists of necessary evidence to be submitted for review. There is a periodic review of cases, which usually takes place, depending on diagnosis, every 3 to 5 years. Lifelong disability is recognized in some cases of severe injury and/or in elderly patients. Childhood patients eligible for "invalidity" status receive a certificate of disability that is valid until 16 years of age, after which the commission reviews the case.

National registries

Following the Chernobyl accident, the All-Soviet-Union Registry of Persons Exposed to Radiation was established in the summer of 1986. After the collapse of the USSR in 1991, national Chernobyl registries were set up in Belarus, Russia and Ukraine.

For the purpose of data collection, registries have been established at the national, regional and district levels. Special protocols and forms were developed in order to unify the information collected in the three countries. These documents concern registration, clinical examination, dosimetry, and correction forms. The registered persons comprise four main groups:

- Group 1: Persons involved in the clean-up operations at the Chernobyl Nuclear Plant (liquidators).
- Group 2: Persons evacuated from the exclusion zone in 1986.
- Group 3: Persons resident in the territories monitored (relocation zone) or resident there immediately after the accident.
- Group 4. Children born to parents in Group 1 in Russia or in Groups 1-3 in Belarus and Ukraine.

As of 2003, the Chernobyl registry in Russia includes more than 192,000 emergency workers and about 360,000 residents of the four contaminated oblasts of Russia, which include Bryansk, Kaluga, Oryol and Tula (Ivanov, 2004). In Ukraine, the Center for Information Technologies and National Registry includes information on 291,000 liquidators, 77,000 evacuees, 1,498,000 residents of contaminated territories, and 294,000 children born to persons exposed to radiation due to the Chernobyl accident (Bebeshko, 2004). In Belarus, the Chernobyl Registry includes records on some 54,000 liquidators (1986-1987), 20,000 liquidators (1988-1989), 6,000 evacuees, 74,000 re-settlers and residents of contaminated territories and about 17,000 children born to persons exposed to radiation (Kenigsberg, 2004). This totals some 3 millions people included in the registries of the three states.

Expert assessment

Consensus

An initial medical examination is useful to identify those persons at risk and categorize them relative to their need for medical care. It is also useful to provide reassurance and information.

Relative to subsequent examination, inclusion of asymptomatic persons with very low doses in a long-term medical follow-up programme may unnecessarily increase anxiety and is unlikely to provide any medical benefit. There is no evidence in the literature that screening and medical monitoring are cost effective or helpful at lower absorbed radiation doses. Data on mortality and morbidity presented elsewhere in this report do not show that annual screening or medical monitoring has had any effect on these outcomes, except possibly in the case of thyroid cancer.

WHO does not currently recommend annual physical examinations for asymptomatic persons. The primary concern at absorbed dose levels below 1 Gy is development of cancer and leukaemia. At present the only cancer screening tests recommended by WHO are mammograms for breast cancer and PAP smears for cervical cancer. For most cancers thought to be radiogenic, there are currently no effective screening tests. However, the evidence for the effectiveness of screening for thyroid cancer has yet to be determined.

On the other hand, persons who are symptomatic or have apparent radiation injuries do benefit from medical care. There is a need for continuing clinical care for those with clear radiation injuries. These are usually those with whole-body doses in excess of 1 Gy or local doses in excess of 5 Gy

There are currently very large and extensive programmes in place in the three affected countries for medical evaluation and follow-up of liquidators, those living in contaminated areas and children born to parents who were exposed to radiation. These programmes apparently have not been evaluated relative to continuing need.

Gaps in Knowledge

A lot of medical attention has been directed towards care of highly exposed liquidators. Identification of interventions that have proved most effective would greatly enhance medical care in case of future radiation accidents.

There has been a lot of screening for thyroid cancer. Whether these have had an impact on ultimate outcomes or quality of life is not clear at the present time.

In some screening programmes, there has been an attempt to identify subsets of persons who might be particularly susceptible to certain diseases, such as leukaemia. It is not known whether these programmes will ultimately be effective.

It remains unclear whether being under continuous medical monitoring and being recognized as a Chernobyl "invalid" are beneficial for population health or may have a negative psychological impact.

The issue of lenticular opacities has been dealt with elsewhere in this report. It would be useful to periodically evaluate follow-up programmes dealing with cataract.

Recommendations

Medical care and annual examinations of highly exposed liquidators should continue.

Current follow-up programmes for those persons with exposures less than 1 Gy should be re-examined relative to necessity and cost-effectiveness. From previous knowledge, these follow-up programmes are unlikely to be cost-effective or beneficial to individuals. Extensive examinations by teams of experts and blood and urine examination on an annual basis seem to be unnecessary. Better targeted programmes are needed to reduce infant mortality, promote healthy lifestyle and nutrition, prevention and early-detection of cardiovascular diseases, and to improve the affected population's mental health.

Sensitive populations known to be particularly vulnerable (e.g. children exposed to radioiodine) should be considered for specific screening (e.g. for thyroid cancer).

Screening for thyroid cancer should continue for the time being, but should be evaluated for cost/benefit. This is important, because as the population ages, many additional benign lesions will be found, and there is a risk from unnecessary invasive procedures.

Registries of exposed persons should continue, as well as studies of morbidity and mortality. These are typically for documentation or research purposes and usually will not be of a direct medical benefit to the individuals.

When a new scientific technique or findings are discovered that may play a role in ameliorating potential radiation effects, targeted research studies should be continued or initiated.

Any medical follow-up studies should be conducted with an estimation of individual absorbed radiation dose to the tissue of interest, appropriate control groups, and assessment of confounding factors.

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APPENDIX 2
CHERNOBYL FORUM EXPERT GROUP HEALTH MEETINGS:

Chernobyl Forum Expert Group Health Meeting on Thyroid Studies
1-3 December 2003, WHO, Geneva.

Chernobyl Forum Expert Group Health Meeting on Leukaemia and Solid Cancer Studies
5-7 April 2004, WHO, Geneva.

Chernobyl Forum Expert Group Health Meeting on Studies of Non-Cancer Effects and Health Care Programmes
13 - 15 September 2004, WHO, Geneva

Chernobyl Forum Expert Group Health Editorial Meeting
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