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Assessment of Radiation Exposure in the National Cohort

Recommendation by the German
Commission on Radiological Protection

Adopted at the 259th meeting of the German Commission on Radiological Protection, on 13th/14th December 2012

The German original of this English translation was published in 2012 by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety under the title:

Erfassung der Strahlenexposition in der Nationalen Kohorte

Empfehlung der Strahlenschutzkommission

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1 Introduction

A project sponsored by the Helmholtz Association, the German Federal Ministry of Education and Research (BMBF) and the German *Länder* plans to establish a National Cohort that will provide data for epidemiological studies of the influence of environmental factors and lifestyle on the development of disease. It is envisaged that two hundred thousand participants will be recruited for the cohort. The National Cohort may help to provide information on two key issues relating to protection against ionizing radiation.

The first of these issues concerns the age-related distribution of exposure to ionizing radiation in the German population. Because disease risk is age-dependent, this is particularly important for assessment of the late effects of radiation exposure. However, it is not yet clear whether medical, natural[1] and occupational exposure to radiation can be determined with sufficient accuracy in the National Cohort.

The second issue concerns assessment of the possible health risk from low-level exposure to radiation, which for the purposes of this report is defined as an effective dose of between 10 and 100 mSv. This is usually taken to be a dose in addition to the average exposure to radiation, which is not itself defined. Furthermore, the National Cohort provides an opportunity to study possible health differences between cohort members exposed to relatively high levels of radiation and those exposed to relatively low levels; as part of this investigation, the study will seek to assess total exposure from medical, natural and occupational sources. Even if the studies do not yield a statistically significant answer to the question of risk, it will be possible to make a statement in the form *“the risk is less than …”.* The issue of the risk of cancer as a result of low doses of ionizing radiation is one that is coming under renewed scrutiny as a result of recently published studies (Ozasa et al. 2012; Pearce et al. 2012).

One of the tasks of the thematic working groups that were set up during the planning phase for the National Cohort was to prioritize issues and investigations. Radiation research was assigned to the “Environment” working group. Assessing radiation exposure was categorized as important. However, the working group was uncertain whether radiation exposure could be assessed with the necessary precision or estimated from the available data. The Epidemiological Planning Committee, which was responsible for defining the study programme, likewise classed radiation exposure as important and recommended preliminary studies. As a result of this recommendation, “Pretest 1” studies were conducted to reconstruct medical exposure and to measure natural and technologically enhanced natural external radiation exposure. A separate study to reconstruct doses resulting from medical exposure was carried out at Augsburg Hospital (Klinikum Augsburg).

In the present recommendation, the German Commission on Radiological Protection (SSK) puts forward its view on whether it can be assumed that the new data situation will enable radiation exposure in the National Cohort to be assessed with a sufficient degree of accuracy.

[1] All subsequent mention of natural radiation exposure in this report should be interpreted as including technologically enhanced natural external radiation exposure even if this is not expressly stated.

2 The National Cohort

The National Cohort (Wichmann et al. 2012) has four general objectives:

– to investigate the causes of chronic diseases and their links with genetic, lifestyle and environmental factors.

– to identify new risk factors and investigate existing geographic and socio-economic disparities in health status and disease risks in Germany.

– to develop risk prediction models for chronic diseases and identify effective prevention methods (personalized prevention strategies).

– to identify opportunities for early detection of chronic diseases (evaluation of markers as effective tools for disease prevention).

Particular attention will be paid to the following chronic diseases in the National Cohort: cardiovascular diseases (especially heart attack and stroke), diabetes mellitus, cancer (especially breast, colon, prostate and lung cancer), neurodegenerative and neuropsychiatric diseases (especially dementia and depression), respiratory diseases (especially chronic obstructive pulmonary disease (COPD) and asthma) and infectious diseases (especially respiratory, gastrointestinal and oral infections). The study will examine not only clinically manifest diseases but also subclinical phenotypes (e. g. by measuring cognitive function, lung function or the intima-media thickness of the carotid artery) and functional changes (e. g. through musculoskeletal examinations). The risk factors and exposures that will be taken into account include lifestyle factors (e. g. physical activity, fitness, diet and nutrition), psychosocial and socio-economic factors, genetic factors and environmental conditions. Examples of specific research questions that will be addressed with the help of the National Cohort can be found in the Scientific Concept of the National Cohort (www.nationale-kohorte.de).

Starting population and study region

The study population for the National Cohort will be recruited through 18 study centres distributed throughout Germany. At each of the centres, a random sample of the general population in the age range 20-69, stratified by age and gender, will be drawn from the regional resident registration registers. The Cohort will consist of 200,000 individuals, of whom 100,000 will be women and 100,000 men.

In the cohort the age groups 20-29 and 30-39 years will each represent 10 % of the total; each of the three older decades will contribute 26.7 % to the total. The greater proportion of participants in the 40-69 age range is justified by the fact that rarer cancers and other less common diseases are likely to occur in sufficient numbers only in these age groups. Early stages of disease (intermediate phenotypes, early function changes, subclinical diseases) will receive particular attention in the younger age groups. The age and gender distribution will be the same at each study centre.

Definition of the scope of the study was based on estimates of the expected number of new cases of important diseases and the frequency and distribution of important risk factors. Decisions were of course also influenced by financial considerations.

The study programme

The planned term of the National Cohort is 25-30 years (or more). Funding is currently assured for the first ten years.

- At the *baseline assessment*, carried out at the study centre, participants will answer detailed questions, undergo medical examinations and be asked to provide samples of biomaterials. Questioning will involve a computer-assisted personal interview and completion of questionnaires (mainly electronic). Questioning of all 200,000 cohort members will take approximately five years.
- Each cohort member will undergo *re-assessment* approximately five years after the baseline assessment. The re-assessment will essentially involve repetition of the baseline assessment programme, so that changes can be detected.
- In addition, all cohort participants will be re-contacted every 2-3 years for the term of the National Cohort and asked to complete a postal questionnaire for purposes of *follow-up monitoring.* Diseases that come to light in the course of follow-up can then be linked to data collected earlier at the baseline assessment or at a re-assessment.

At the *baseline assessment and re-assessments*, information will be gathered on socio-demographic factors, lifestyle (e. g. physical activity, smoking, diet and nutrition, occupation), psychosocial and socio-economic factors, medical history and family history.

The *baseline assessment and re-assessments* involve in addition to a physical examination a comprehensive programme of physical function measurements (heart, circulation, lung function, etc.) and collection of biomaterials such as blood, tissue, urine, saliva and stool samples and nasal swabs. The samples will be stored long-term in a central biobank with decentralized back-up storage. The protocols for taking samples and storing aliquots will be designed to permit the greatest possible range of options for future laboratory analysis, including chromosome analysis. In addition, fitness and cognitive functions will be measured.

At *follow-up monitoring*, which will take place for all participants every 2-3 years, cohort members will be asked to fill in short questionnaires designed to capture changes in lifestyle and other health-related characteristics (use of medications, smoking, menopausal status, selected disease symptoms) and the occurrence of selected important diseases (“active” follow-up). Important details will be verified by cross-checking with medical documents. In the case of cancers there will be comparison with existing cancer registries (“passive” follow-up). In parallel, a mortality follow-up will be performed every 2-3 years using resident registration registers.

In addition to the study programme that is already planned, it may be possible to carry out other investigations, provided that additional funding is made available for them.

3 Assessing radiation exposure

The principal components of exposure to radiation in the German population are medical, natural and occupational radiation exposure. Assessing the risk to health of ionizing radiation in the National Cohort requires not only prospective assessment of exposure to radiation but also retrospective assessment from birth up to the time of entry into the Cohort.

3.1 Medical exposure

The use of ionizing radiation in medicine has major diagnostic and therapeutic benefits for patients. Late effects of diagnostic procedures involving low doses of radiation are rare. However, the associated risk is not at present quantifiable. Quantification of the risk would be a useful aid to choosing which procedure to use.

A feasibility study of the retrospective determination of medical radiation exposure is currently being carried out through the Environmental Research Plan of the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU). In addition, a study designed to reconstruct heart doses and hence provide information on the feasibility of reconstructing organ doses has been completed at Augsburg Hospital (Klinikum Augsburg). The present findings of the two studies (Zeeb et al. 2012, Höck 2012) are summarized below.

Feasibility study of retrospective determination of medical exposure

The feasibility study focused first on retrospective assessment of previous exposure in the course of medical assessment in 199 participants at the study centres in Bremen and Hamburg. As part of the study, a questionnaire developed on the basis of systematic research was administered while basic medical and epidemiological data was being collected in a personal interview. In principle, collection of the requisite data was found to be feasible and the associated time requirement was on average moderate. All the participants in the feasibility study provided detailed information about previous diagnostic investigations involving radiation exposure. In some cases it was difficult to pinpoint the exact time period in which the investigations had been carried out. There is also some doubt as to whether computerized tomography (CT) and magnetic resonance tomography (MRT) can always be clearly distinguished, although a personal interview provides a good opportunity to make participants aware of the technical differences between the two.

Various methods of establishing estimated organ doses or effective doses were considered. Since exact investigation parameters are not available in the case of retrospective assessment, it is necessary to use standard values in accordance with the German X-ray Regulation (Röntgenverordnung), which defines diagnostic reference levels, together with conversion factors. CT doses were estimated using the program CT-Expo (Stamm and Nagel 2002). A key finding of the questionnaire and dose estimates was that all the participants surveyed had undergone diagnostic X-ray examination; some 45 % (90/199 of those questioned) had also undergone CT examination. The most frequently examined organs and regions were the teeth, chest and extremities. Dose estimates were available only in the form of estimates for individual organs. The average lung dose from a conventional X-ray of the chest was 0.11 mSv. The average total head dose from CT examination of the skull was estimated at approx. 52 mSv.

The study also considered whether prospective assessment could be conducted using special X-ray record cards on which details such as the dose-area product and the dose-length product could be entered. Here it was found that attempts to record these details have in practice tended to be unsuccessful.

Overall the participants in the feasibility study provided detailed information on previous diagnostic investigations involving exposure to radiation. Work on validating the information provided by participants against billing information held by health insurers is currently under way.

Study of retrospective determination of heart doses from medical exposure

When analysing the risks associated with the medical use of ionizing radiation, it is important to have information on equivalent doses in organs and tissues that are sensitive to radiation. Dissertation work carried out at Augsburg Hospital looked at retrospective determination of heart doses from medical exposure. The study gives some idea of the feasibility of reconstructing organ doses. The findings of the Augsburg study are categorized according to the different types of radiation use in medicine:

Conventional X-ray diagnosis: Organ doses resulting from X-ray examinations are calculated from settings and measurement data laid down in the German X-ray Regulation (Röntgenverordnung) and appliance-specific values in combination with dose conversion factors. The conversion factors are obtained from Monte Carlo calculations using voxel phantoms or from numerical phantoms. However, this type of data is often no longer available for retrospective dose assessment. To estimate heart doses received during previous investigations, therefore, time-dependent dose factors were calculated; current dose levels were then multiplied by these factors. Using optimum dose levels that take account of technical progress and a categorization of work quality, a matrix of correction factors for different periods was then drawn up for the years 1946-1995. After 1995, information on dose development can be obtained from the information on diagnostic reference levels (DRLs).

Computer tomography (CT): Especially in the early years, technical development of CT machines after 1975 focused more on improving image quality and extending the scope of investigations than on dose reduction. Between 2003 and 2010, doses were nevertheless cut. The dose factors used in the Augsburg study reflect the changes in DRLs.

Angiography (PTCA): Cardiological dose protocols document not only the specific angle settings but also the associated dose area product (DAP), the irradiation time with DAP and a total DAP. This information can be used in combination with appropriate conversion factors to estimate a heart dose for individual investigations.

Nuclear medicine: The additional activity associated with heart investigations and the resulting heart dose can be calculated using conversion factors published by the International Commission on Radiological Protection (ICRP; ICRP 1988, ICRP 1998). For investigations in the field of nuclear medicine, a relatively simple dosimetry concept is therefore available. For purposes of retrospective assessment, this concept was modified to take account of historical changes in the activity prescribed and the nuclides used. If personal biokinetic data have been collected for a patient (e. g. during treatment or functional investigations), this can be taken into account.

Radiotherapy: Because of inhomogeneous dose distribution, organ doses cannot be determined retrospectively without individual post-processing on the basis of the relevant radiation data.

The Augsburg study has shown that even if the available investigation or dose protocols are incomplete, so that individual doses cannot be estimated, it remains possible to specify mean values and the associated uncertainty range. If data is available and complete, individual dose estimates should always be calculated. For the different investigation types, the uncertainties arising from the various dose estimation methods used were described and compared. This makes it possible to provide an indication of the degree of uncertainty associated with the results of the dose assessment for individual participants in the study. The process is relatively complex, but it could be made available to all the study centres by developing appropriate software. It would also be possible to collect data in the individual study centres but carry out dose estimation centrally. Dose estimation can and should be carried out at least for those cohort members who can be assumed from the questionnaire results to have experienced relatively high radiation exposure.

3.2 Natural radiation exposure

Natural radiation exposure comprises exposure through inhalation of radon and its progeny, internal exposure through incorporation of other radionuclides and external exposure including exposure to technologically enhanced natural radiation.

The risk of lung cancer arising from inhalation of radon and its progeny has been well researched (ICRP 2010). Assessment of exposure to radon in the National Cohort is unlikely to make any significant contribution to the state of knowledge.

Since exposure to radon can significantly increase the risk of lung cancer, the lung cancer risk as a result of radiation exposure cannot be studied in the National Cohort if exposure to radon is not assessed. By contrast, the leukaemia risk in the National Cohort can be studied if the uncertainties arising from the variability of radon exposure are taken into account. Assuming a conversion coefficient of 0.3 mSv/year per 100 Bq/m^3 (SSK 2008a) and a mean radon concentration in German homes of 50 Bq/m^3 (SSK 2008a), the mean bone marrow dose is 0.15 mSv/year. This is significantly lower than the dose to the red bone marrow from terrestrial radiation.

In Germany the variability in internal radiation exposure as a result of food consumption is usually low by comparison with the variability of external radiation exposure. The influence of food consumption on overall dose distribution is not large enough to justify the extensive work involved in collecting the corresponding data for a very large number of people. However, the uncertainties that arise because the ingestion dose has not been assessed need to be taken into account when analysing the National Cohort data.

The SKK has estimated that the effective dose to the German population from external exposure is typically between 0.5 and 1.2 mSv per year (SSK 2008b). The dose received by the age of 70 can therefore vary by an amount in the order of about 50 mSv. A large part of this variability arises from differences in the gamma dose rate in houses and flats of differing construction and geographical location and differences in the amount of time spent in a particular building; this cannot be captured by mean regional dose levels.

The SSK has also calculated that including exposure to internal radiation from other radionuclides apart from radon does not significantly alter this range of variation.

Test study to determine external radiation exposure

In a test study conducted by the Helmholtz Centre in Munich, bracelet dosimeters were distributed to 15 participants in a feasibility study for the National Cohort at the Augsburg study centre and to five members of the centre’s staff. Shortly before the interview with the participant, the beryllium oxide dosimeters were reset to zero by illumination. Participants were instructed to wear the bracelet for four weeks, then cut it off and return it to the researchers by post together with a questionnaire. The questionnaire captures information about travel, especially air travel, and about medical and occupational radiation exposure while the bracelet was being worn; the measurement data can then be analysed in the light of this information.

Of the 20 bracelets that were distributed, 18 could be analysed. Improvements to the bracelet are expected to increase the success rate. One of the participants had had an X-ray of the thorax. His dosimeter reading was significantly higher than the readings of other participants. Extrapolation of the other 17 readings to a year yielded effective doses of between 0.60 and 0.91 mSv. For that extrapolation, the neutron component of cosmic radiation, which is not captured by the dosimeter, was estimated at 0.1 mSv/year. The uncertainty of the readings was expressed in a relative standard deviation of approx. 8 %. Planned improvements to the measurement system will reduce the measurement uncertainty. The usefulness of the bracelet dosimeters was due to be evaluated in the autumn of 2012 in a second, enlarged feasibility study (200 participants) at four study centres with differing average local dose rates.

3.3 Occupational radiation exposure

The number of cohort members who are exposed to radiation at work is likely to be relatively small. The SKK has estimated this number as follows.

Approximately 55 million of Germany's population of around 82 million are within the age range of the National Cohort (20-69 years). If one assumes that all the 350,000 people on the German Radiation Protection Register are in this age range, these people represent 0.7 % of the total population. Of the 200,000 participants in the National Cohort it can therefore be expected that 0.7 % or 1,400 people will be on the register. About 20 % of these people – or 300 individuals – will be exposed to levels of radiation at work that are above zero, averaging 1 mSv/year.

Data on occupational radiation exposure can be obtained from the German Radiation Protection Register. Separate investigations can be carried out for the expected number of approx. 300 people exposed to radiation at work. Issues relating to the treatment of radiation levels below the detection limit need to be clarified.

4 Statistical usefulness

The SSK believes that it will be possible to use National Cohort data to estimate the upper limit of a confidence interval. In connection with estimating this upper limit the SSK has made assumptions appropriate to an indicative calculation. Some of these assumptions are not appropriate for a statement about existing risks. This applies in particular to the use of the effective dose. A risk calculation should be based on organ doses and organ-specific risk values. The assumptions made are:

– Data on the radiation exposure of all 200,000 members of the National Cohort will be collected.

– The follow-up period is 15 years. During this period, 10,000 cases of cancer will occur in the cohort.

– The mean effective dose of the third of the cohort members with the highest cumulative dose from birth to the end of the follow-up (minus minimal latency time) is 30 mSv higher than the mean dose of the third with the lowest doses. The calculation is carried out to compare these two groups. The value of 30 mSv was adopted here because i) the feasibility study on retrospective determination of medical exposure found that a relatively large number of participants questioned had already undergone several CT investigations, and ii) given an age at onset of illness of 70 years, doses of external exposure from natural sources may vary by 50 mSv. It is not yet clear how big the dose differences in the National Cohort will actually prove to be.

– Given a dose difference of 30 mSv and the expected age distribution in the two groups of cohort members, the excess relative risk (ERR) for cancer other than lung cancer is 0.0135 (assuming a linear dose-effect relationship in the range 30-2,000 mSv with a gradient of 0.45 Sv^{-1}, as was observed at the higher end of this dose range among Japanese atom bomb survivors).

The outcome was an upper 95 % confidence limit for the ERR at 30 mGy of 0.0475. This means that for a follow-up period of 15 years the likelihood of the ERR being higher than the best estimate of the risk at 100 mGy can be ruled out with a probability of almost 95 %. If the observation period were longer, more extensive statements could be made.

This is an indicative estimate only; it is influenced by the assumptions made and the statistical model used. It was not possible to take uncertainties other than statistical ones into account in the power estimate.

5 Evaluation and recommendation

Participants in the feasibility study on reconstructing the medical radiation exposure of National Cohort members provided detailed information about previous medical use of ionizing radiation. This information has not yet been validated against health insurers' billing data, but this validation is currently being undertaken as part of the feasibility study. Collection of data from the National Cohort will at least make it possible to determine the frequency distribution of the medical use of ionizing radiation in the German population.

The dissertation at Augsburg Hospital (Höck 2012) has shown that it is still possible to attribute mean values and the associated uncertainty limits even if the available investigation records or dose protocols are incomplete, so that individual doses cannot be estimated. The procedure can, for example, be applied to those cohort members for whom on the basis of the questionnaire results relatively high radiation exposure can be assumed.

It is possible to assess equivalent doses from natural and technologically enhanced external radiation exposure in the National Cohort by asking participants to wear bracelet dosimeters for a period of four weeks. Measurement of radon exposure, by contrast, is less appropriate on account of the complexity of the task, and because of the good state of knowledge of the lung cancer risk from radon exposure it is not necessary. However, establishing the biorepository will make it possible to investigate the biological effects of radiation exposure in humans. Information on radon exposure could be useful in this connection.

An indicative appraisal of the statistical usefulness of a study of cancer (except lung cancer) after radiation exposure in the National Cohort showed that for a dose difference of 30 mSv it is highly likely that after an observation period of 15 years a risk greater than that currently assumed at 100 mSv can be ruled out. The study could therefore make an important contribution to the validation of previous risk estimates for the low-dose range – a validation that assumes particular significance in the light of the higher risk levels of low doses that have recently been published. However, it is not known whether the dose difference between high-exposure and low-exposure cohort members will amount to 30 mSv, and uncertainties other than statistical ones were not taken into account in this appraisal.

There are in principle other methods – such as the use of information from health insurers and cancer registers – that could be used to describe the distribution of medical radiation exposure in the population and evaluate the cancer risk. These other approaches have not yet been tried. Their advantage lies in their completeness, the fact that participants' consent is not required and their statistical power. Their fundamental disadvantage is the absence of additional personal information about the individuals to whom the details relate. The strength of a cohort study such as the one involving the National Cohort resides in the fact that the observed exposure can be evaluated in relation to all relevant health endpoints in an overall context that takes account of all other risk factors and exposures such as chronic diseases, occupational exposure and lifestyle factors. To this can be added the opportunities provided by the biorepository.

The SSK recommends retrospective and prospective recording of the organ doses of members of the National Cohort as a result of medical, occupational and external natural radiation exposure for the following reasons. The study has the potential:

- to provide information about the distribution of medical exposure.
- to measure the level and distribution of natural external exposure.
- to collect data on medical, occupational and natural exposure for each individual cohort member that is not available in any other existing cohort.
- to provide an estimate of the upper limit of the confidence interval of the risk from doses that reflect the variability of doses from all exposure to ionizing radiation (except radon) in the German population.
- to create a dataset with a wide range of behavioural and health parameters that in combination with exposure information could be very useful for future investigations.

In view of the open questions that have been described in relation to

- validation of the reconstruction of medical exposure,
- the expected dose distribution among cohort members, which is key to the statistical usefulness of the study,
- the uncertainty of the dose estimates and their impact on the risk assessment

the SSK recommends that the next step should be to use the baseline assessment of the National Cohort for a larger feasibility study (several thousand participants) of the determination of organ doses from medical use of ionizing radiation and from occupational, natural and technologically enhanced radiation exposure. The information on medical radiation exposure provided by cohort members should, for example, be validated against data held by providers of statutory health insurance. To reconstruct the exposure of people with higher levels of medical exposure, medical records should also be evaluated. X-ray record cards should be issued as part of the feasibility study; during follow-up their use should be checked and reminders issued. The uncertainties about dose distribution that arise because radon exposure is not measured and data on internal exposure as a result of food consumption is not collected should be taken into account when analysing the data. It is worth investigating whether questions about building characteristics can be asked in such a way that collection of information on radon exposure becomes possible. Consideration should also be given to collecting some basic information on radiation exposure for all 200,000 cohort members at the time of the baseline assessment. Finally, the costs and benefits of capturing radiation exposure in the entire cohort should be discussed.

The later assessment of radiation exposure in the entire National Cohort during the follow-up investigation would then have the advantage that the procedure used would have been validated. For the subgroup investigated in the feasibility study, the time history of medical and natural external radiation exposure can be determined.

The SSK also recommends that other European countries be encouraged to collect information on radiation exposure in their national cohorts with a view to later pooling of the data. Cooperation with other large European cohorts (UK: 500,000, SE: 500,000, FR: 200,000, NL: 160,000) could provide a broader statistical basis with more than one million participants and potentially make a genuine risk assessment possible rather than simply an estimate of the upper limit of the confidence interval.

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