

The Agenda for Research on Chernobyl Health (ARCH) Strategic Research Agenda (SRA)

Advice of the MELODI expert group November 2011

The Agenda for Research on Chernobyl Health (ARCH) group of experts has conducted a profound analysis of the status of radiation risk research after the Chernobyl accident and of scientific needs for improving the basis of radiation protection in Europe. They identified the great prospects of present and future studies of populations exposed by the Chernobyl accident. Their recommendations are summarized in a Strategic Research Agenda (SRA) issued at the beginning of 2011 (see Annex).

An improvement of our understanding of health risks from exposure with low doses needs large, high-quality studies integrating epidemiology, dosimetry, radiobiology and modeling. Whereas a wide range of possible studies and interesting objectives were listed by the ARCH group of experts (see Annex), it is recommendable to **focus on a limited number of studies** in order to allow for a sufficient financial endowment of these studies. Targeted research of some health effects of the Chernobyl accident should be supported.

In agreement with the ARCH SRA, we consider that the **major priorities are the lifespan follow-up of liquidator and exposed children cohorts**. These studies are of high relevance to radiation protection issues, and their features provide a real opportunity to overcome some of the classical limitations (existing individual dosimetric data and possibilities of improvement, possibility of specific nested study design to collect additional information, possibility of combined analyses to increase power...). A **cohort of liquidator's offspring** also appears worthwhile if the doses of the workers (including dose to the gonads) and the dose of the offspring can be reconstructed.

A better coordination of the different projects is needed to improve the quality of studies and increase their capacity to bring new knowledge about low level radiation exposure effects. A main recommendation of the ARCH group of experts is to set up a Chernobyl Health Effects Research Foundation (CHERF). The **creation of a coordination body with a long term support** to ensure the follow-up of the cohorts is a timely recommendation in order to exploit the potential of radiation risk research in the aftermath of the Chernobyl accident. The role of such coordination body should be clearly defined, and its implementation must not delay the start of research programs, due to lengthy negotiations. Creation of a CHERF is a very attractive concept, but a proper scientific management might be also implemented through a smaller coordination board.

An initial step in order to implement the suggested research program will be to **obtain/maintain agreements** with the Governments of Belarus, Russia and Ukraine as well as with the US National Cancer Institute (NCI) and the research bodies involved. Pertinent contacts should be initiated as early as possible. The completion of the needed agreements could constitute a decisional milestone for the continuation of the long term support.

Many other epidemiological studies present a real capacity to improve our understanding of health risks associated to low doses. These include studies of occupationally (nuclear workers, uranium miners, medical staff...), medically (CT scans patients, therapeutic irradiations...) and environmentally exposed populations (Ozyorsk and Techa river residents, high background radiation areas...). Support to Chernobyl studies must be **integrated into a general research framework** to provide a coherent support to radiation protection in complement to other scientific data, particularly those obtained from the A bomb survivors follow-up.

IS THE ARCH PROPOSAL PERTINENT?

The ARCH proposal appears pertinent by two aspects:

- Long term follow-up of exposed populations is needed to determine the distribution of radiation induced risk over the lifespan. Many health effects present a latency of several decades between exposure and occurrence, and could not be considered if follow-up stops now. **The ARCH proposal of a funding mechanism for long term support of studies is a timely recommendation.** Long term studies of Chernobyl exposed populations should provide pertinent results regarding major current issues in radiation protection: quantification of the shape of the dose-response relationship for cancer at low levels of dose, non cancer effects of radiation exposure (cardiovascular diseases, cataract), risks associated to internal contamination and potential inherited radiation effects.
- Numerous projects are ongoing to evaluate the consequences of the Chernobyl accident, with different protocols, data quality and management processes. **A better coordination of projects is needed** to ensure comparability of results and to allow large scale combined analyses. Quality check, data validation, obtaining and maintenance of agreements (ethics committees, authorities, agreements between partners) and sustainable funding processes need a coordinated and structured organisation. The creation of a clearly defined coordination body should provide a comprehensive solution to ensure a sustainable support to studies.

IS THE ARCH PROPOSAL FEASIBLE?

Management aspects

- **Contractual agreements:** no progress could be made without an initial approach to the US NCI, followed by approaches to the authorities in Belarus and Ukraine to see whether current US funded programmes in those countries which are being scaled back could be extended as joint programmes with the EC. Some political risks associated with collaboration with the three countries most affected by the Chernobyl accident should be envisaged. Agreements between contributing research teams are also an important step.
- **Ethical agreements:** a review of agreements from pertinent ethics committees is needed for the continuation of epidemiologic studies. Additional agreements may be needed regarding collection of biological samplings. Also, combination of data from different countries may pose problems related to compatibility of databases, property of data, anonymous identification of people, agreements from data protection committees. Control of these aspects should be facilitated by the creation of a coordination body.
- **Coordination body:** The creation of a CHERF foundation is a very attractive concept. Nevertheless, there is concern that the creation of such foundation may delay the start of important research programs, as it will need lengthy negotiations of the EC with other parties (the US NCI, the governments of the affected countries). These negotiations should be launched as soon as possible, and valuable research projects should be started as soon as possible, without waiting for these negotiations to be concluded. A proper scientific management might be also implemented through a kind of smaller Chernobyl Research Advisory Board with a long term financial support. The role of such coordination body also has to be clarified. Its main role should be to ensure a sustainable follow-up of lifespan cohorts, on which specific research projects can be implemented.
- **Feasibility milestone:** The ARCH group of experts recommended support for an initial 10-year period. This long term request could be accompanied by a feasibility

period of 1 or 2 years terminated by a milestone to decide to continue or stop financial support. The objectives could include:

- Completion of needed conventions between partners: Ukrainian, Belarusian, Russian authorities, US NCI, EC and other funding bodies, clinics and research teams involved in the project;
- Obtaining of ethics agreements;
- Review and verification of data quality for identifiers, diagnoses, doses;
- Review and verification of data quality for tissue/blood samples.

Epidemiologic aspects

- Several well known limitations are regularly opposed against the continuation of Chernobyl epidemiological studies: selection bias, loss to follow-up, exposure misclassification... Some of these **limitations should be overcome** at least partially, thanks to the ARCH proposal. The studies herein recommended as high priorities present the best features for a long term follow-up. The quality of the studies (quality of follow-up, quality of dosimetric reconstruction, harmonisation of diagnoses, collection of biological material) could be ensured in the future if an adequate funding process is implemented for sustainable support. The implementation of specific research protocols nested in these long term cohorts, especially, nested case-control studies, could allow improving data quality and collecting additional information. Also, a better coordination of studies will allow performing combined analyses and then improving the statistical power to detect low excess risks.
- For some other studies, considered of less priority, **epidemiological limitations seem difficult to overcome**. For example, for *in utero* or pre-conceptional exposure, the feasibility to recover some data retrospectively is highly improbable if not already collected. Monitoring of cancer rates in the general population may be interesting to conduct ecological studies (for example for breast cancer), but its contribution to a better understanding of radiation effects is expected to be poor, as it will be very difficult, if not impossible, to disentangle radiation effects on cancer rates from other factors. Also, nation-wide or Europe-wide studies of cancer or other disease incidence trends seems of little promise regarding the determination of the radiation induced health effects just because average national radiation doses are low.

Dosimetric aspects

- Studies can be classified according to dosimetric aspects:
 - studies for which an **individual dosimetry** approach has already been established (though it should be improved): cohorts of liquidators (registered external dose) and exposed children (thyroid dose). Priority should be given to this category of studies;
 - studies that do not require individual dosimetric estimates: monitoring of incidence and mortality cancer trends;
 - studies for which dosimetry may be a major roadblock, i.e. where either the feasibility of reconstructing individual doses must be evaluated or for which considerable efforts (scientific and economical) would be needed: subjects exposed *in utero*, evacuees.
- The feasibility of gathering dosimetry data from the registries (for the clean up workers), from the passport doses (for the population of areas with higher radionuclide deposition) and from estimates of cumulated doses validated with individual thermo-luminescent dosimeters and whole body counting measurements and their reliability should be evaluated before starting any project. Surprisingly, the ARCH SRA did not give any importance or priority to the **inventory of dosimetric information** that was proposed in the first ARCH document (Proposals for urgent priorities, see Annex).

- **Dose reconstruction from internal contamination:** several studies have shown that dose from radionuclides ingested through the diet should be reconstructed on an individual base and should include both short and long lived sources of exposures.. These studies would require significant efforts.
- **Uncertainties in dose** estimates are reported as being between 25% (for external dosimetry, when the personal dosimetry is considered reliable) and a factor of 11. Further researches should focus on the quantification of relevant uncertainties, and to the analysis of their potential impact on risk estimates.

Biological aspects

- The establishment of the **Chernobyl Tissue Bank** (CTB) has been made possible through a combined financial support from the governments of Ukraine and Russia, the EC, the US NCI and the Japanese Sasakawa Memorial Health Foundation. This illustrates the feasibility of a combined sustainable support process. The CTB currently gathers samples from thyroid cancer tissue from the Ukr-Am study.
- The ARCH SRA recommends the possibility of creating a tissue bank specifically for the Chernobyl related projects, of encouraging each project to store its own samples, or of collaborating with the existing CTB. A **review of existing samples**, especially among liquidators, and check of their quality has to be performed. Usefulness of these biological samples regarding the identification of pertinent biomarkers should be evaluated. The feasibility of collecting new biological samples should be investigated among individuals with available personal dosimetric data.

WHAT ARE THE MAIN STUDIES TO BE SUPPORTED?

A large number of studies, potential or already ongoing, are considered in the ARCH technical report (see annex). In agreement with the ARCH SRA, **we consider that the lifespan follow-up of liquidator and exposed children cohorts are the major priorities.**

- **Cohorts of liquidators** have a large potential for studying health effects of protracted exposures with cumulative doses in the low and moderate dose range (up to 500 mGy). Cohorts already exist in Russia, Belarus, Ukraine and in the Baltic countries. Especially, workers in Russia and Ukraine generally have higher and better registered/recorded doses, and can be well followed through the National registries. The creation of a coordination body will have for aim to achieve a comparability of study designs, to ensure high quality and complete follow-up, and to improve dosimetry. Based on initial feasibility studies, pooling of the suitable cohort studies will be an important aim to achieve high statistical power. Many tens of thousands of workers with registered doses can be involved in the further research. These studies will provide a basis for implementing specific analytic designs. It should allow evaluating the expression of cancer (leukemia, thyroid and other solid cancer) and non cancer risks (cardiovascular diseases, cataract) over lifespan among adults at the time of exposure, and quantifying the relationship with external and internal radiation exposures.
- **Cohorts of exposed children** (Bel-Am and Ukr-Am studies) are outstanding because of individual measurements of thyroid dose, a regular screening since 1998, and the availability of samples of thyroid cancer tissue in the CTB (partially). These are unique preconditions to explore interactions of genetic factors and radiation, identify markers of radiation induced thyroid cancer and derive characteristics of radiation risks. Even if the statistical power of these studies will remain limited, they should allow evaluating the molecular evolution of thyroid cancer over lifespan. Further efforts should aim to extend the tissue bank including other samples than just cancer tissues, and strengthen the radiobiological research in order to allow an

integrative biological approach supporting risk analyses and the identification of radiation markers (if they exist). Extension of this cohort to cancers other than thyroid is of little promise because of unavoidable large uncertainties.

- Exploring the feasibility of a **study of the offspring** of liquidators also appears worthwhile, if a close cooperation between the different cohort studies among liquidators could be realized and if the dose of the workers (including dose to the gonads) and the dose eventually received by the offspring during childhood (including *in utero* dose) can be reconstructed.
- The feasibility of creating a large **tissue bank** is of great interest. Effort should be given to collect samples for individuals for whom precise dose estimates are available. Considering the potential importance of liquidator cohort studies, a decision on supporting such studies should be accompanied by a consideration of a large-scale tissue bank for members of these cohorts. It could be initially considered as an extension of the CTB. Also, it may be pertinent to evaluate a possible connection with the STORE European project.

Other studies were considered of less priority, due to epidemiological (difficulty to identify the population, to complete follow-up or due to low power), dosimetric (lack of individual exposure data, difficulty of retrospective dose reconstruction) or biological (impossibility to collect samples) limitations.

WHAT IS MISSING IN THE ARCH PROPOSAL?

- **Clarification of priorities:** the ranking of priorities vary between the different documents issued from the ARCH project. Remarkably, the dosimetric inventory is described only in the technical report, and is mentioned neither in the SRA nor in the "Proposals for urgent priorities".
- **Role of CHERF:** the role of the proposed foundation regarding ongoing EC projects that include Chernobyl studies (CARDIORISK, EPIRADBIO, CEREBRAD) is not defined in the ARCH proposal. Also, it is not clear how CHERF should be harmonized with future European projects, and what could be the respective responsibilities of CHERF and of the EC regarding future project evaluation.
- **Budget estimates:** no cost estimates are provided in the ARCH documents. This impedes the comparative evaluation of the different projects/studies reviewed. It also limits the evaluation of the interest of the creation of the CHERF foundation in regard to other possibilities (support of the different projects through classical competitive research calls, creation of a smaller coordination board).
- **Position of potential partners:** the project is feasible only if a sustainable collaboration between different partners can be installed. The position of US, Japanese, Russian, Belarusian and Ukrainian authorities and research bodies is missing. For example, the reason why the US NCI decided to stop the active follow-up of the Ukr-Am and Bel-Am cohorts is not given. This information would be important to evaluate whether a continuation is worth.
- **Time schedule:** no agenda is given of the different phases needed to create a foundation and to launch research projects (obtaining agreements, validation of data sources, combination of datasets...).
- **Missing issues:** no mention is made in the ARCH documents of the issues related to birth defect. The frequency of congenital malformation is still an important matter of concern for the general public, and ways to provide answer to this issue should have been integrated in the ARCH reflection (for example on the basis of the Belarusian nation-wide registration system established in the 1970s).

ANNEX

Context of the MELODI expertise

Based on its review of the health consequences of exposure to radiation from the Chernobyl accident, the Agenda for Research on Chernobyl Health (ARCH) group of experts proposed a Strategic Research Agenda (SRA) to implement the long term research studies to be carried out in the future.

The EC has asked the MELODI association to provide an advice about the pertinence to financially support the recommendations from this SRA. This point has been discussed at the meeting of the MELODI Board of Directors in September 2011, and the Board decided to consult a group of experts not previously involved in the ARCH reflexions. This report presents the results of the assessment of the ARCH SRA by this group of experts.

Summary of the ARCH project

The ARCH project was supported by the EC in the FP7-EURATOM-FISSION framework programme (grant agreement FP7-212737). This “support action” received an EC funding of 206 k€ over a 2-year period (November 2008 to October 2010). The project was coordinated by the International Agency for Research on Cancer (IARC, France). Documents were conceived by a core group of four members (K Baverstock (Finland), E Cardis (Spain), A Kesminienne (France) and D Williams (UK)), with the help of a group of 10 European experts. An international group of 8 scientific advisors was consulted to ensure harmonization with other existing or planned activities around the world. Finally, an external peer review group was asked to provide an independent assessment of the SRA. Additional information is available at <http://arch.iarc.fr/>.

Major aims were:

- To review the state of the art and questions arising from Chernobyl;
- To define motivated project proposals;
- To advise on the scientific strategy needed for further research on the health consequences of the Chernobyl accident.

The reflexion essentially focused on the populations most affected by the Chernobyl accident, mainly in Ukraine, Belarus and Russia.

Three documents were delivered:

- Proposals for urgent priorities (deliverable 1, 26 p). This document lists 5 research proposals (out of a total of 26 identified) to be considered as short term priorities: monitoring of cancer trends, trends in infant and childhood leukaemia, molecular epidemiology of thyroid tumours, breast cancer, and radiation induced cataracts in liquidators. Also, feasibility works are recommended to study cardio and cerebrovascular diseases, and to launch lifespan cohort studies among liquidators, among children with measured thyroid activity and among offspring of liquidators and evacuees. The feasibility of creating a large centralized tissue bank from already existing ones is also recommended.
- Strategic Research Agenda (SRA), deliverable 2, 21 p). This document summarizes the main recommendations from the ARCH expert group and the expected impact of the proposed studies, from a scientific and radiation protection point of view. The main recommendation is the creation of a Chernobyl Health Effects Research

Foundation (CHERF) to coordinate future researches and especially two lifespan cohort studies among liquidators and among individuals from Belarus and Ukraine exposed during childhood at the time of the accident. The ARCH expert group also recommends exploring the feasibility of several other studies, such as a cohort of offspring of liquidators, a cohort of evacuees and the creation of a tissue bank.

- Technical report (deliverable 3, 175 p). This document reviews the existing data/studies and their pertinence regarding major endpoints: thyroid diseases, leukaemia and lymphoma, other tumours, cataracts, cardio and cerebrovascular diseases, immunological effects, health effects of acute radiation syndrome survivors, non-targeted effects and mental retardation. It considers several methodological aspects; pertinence and feasibility of Chernobyl lifespan studies, tissue banks, inventory of dosimetric information. A report dealing with radiobiology issues is also included as an addendum.

Epidemiologic studies listed in the ARCH documents

- Chernobyl liquidators: about 600,000 individuals involved as emergency and recovery workers at the reactor site and in the surrounding 30 km zone and to the construction of the sarcophagus, from which about 240,000 individuals involved in 1986 and beginning of 1987, who received potentially important doses from internal contamination. Cohorts exist in Russia, Belarus, Ukraine and in the Baltic countries;
- Exposed children with exposure reconstruction: especially two cohorts in Belarus and Ukraine (Bel-Am and Ukr-Am studies), which include approximately 24,000 children with estimated thyroid doses and collection of thyroid cancer tissue samples;
- Evacuees: approximately 116,000 residents living within the 30 km exclusion zone evacuated in the days after the Chernobyl accident, and over 100,000 residents of contaminated territories of Belarus and Ukraine relocated in the following months;
- Offspring of liquidators and of evacuees: several tens of thousand children have been born to families of evacuees and of liquidators, and could be interesting to evaluate the level of radiation-induced trans-generational genomic instability in the pre-conceptionally exposed F1 (and possibly F2) offspring. About 43,500 are currently registered in the Chernobyl Registries of Russia and Belarus;
- General population of Belarus, Ukraine, and contaminated regions of the Russian Federation: Trends in diseases could be studied using ecological designs, relying on population based cancer registries. Also, the ARCH technical report cites the possibility to analyse leukaemia risk in Europe on the basis of the European Childhood Leukaemia-Lymphoma Study (ECLIS);
- Individuals born at the time of the accident (*in utero*): children born between 26 April 1986 and 26 February 1987 from mothers who were pregnant at the time of the accident in regions of Ukraine, Belarus and Russia contaminated as a result of the Chernobyl accident. Children could be identified from female evacuees or from cancer registries (cases). A population of approximately 4000 children is already involved in the evaluation of mental retardation;
- Survivors of acute radiation syndrome (ARS): several ten/hundred of heavy exposed emergency workers developed ARS and survived. May be interesting for evaluating late health effects of the suppressed immune system following ARS;
- Children treated for thyroid cancer in Belarus, Ukraine and Russia: could prove interesting in determining optimum treatment for childhood thyroid cancer. Such a cohort study is already underway in Belarus.