



EUROPEAN  
COMMISSION

Community research

# CO-CHER

Contract Number: 605302

## DELIVERABLE **D2.1**

### Chernobyl Research Programme

VERSION 1

Start date of project: 01/02/14

Duration: 30 Months

Project co-funded by the European Commission under the Seventh Euratom Framework Programme for Nuclear Research & Training Activities (2007-2011)

Dissemination Level

<b>PU</b>	Public	<b>PU</b>
-----------	--------	-----------

CO-CHER



**CO-CHER**  
**Cooperation on Chernobyl Health Research**

**Chernobyl Research Programme**  
**Research priorities and timetable**

IARC, Lyon, 2016

## TABLE OF CONTENTS

Executive Summary .....	5
1 Background .....	9
2 Research priorities .....	9
2.1 Summary.....	9
2.2 Populations suitable for long-term studies .....	11
2.2.1 Lifespan cohort of liquidators .....	11
2.2.2 Ongoing studies of exposed children with thyroid activity measurements after the accident .....	14
2.2.3 Ongoing research of those exposed <i>in utero</i> .....	16
2.2.4 Feasibility of setting up a cohort of offspring of liquidators and evacuees.....	17
2.3 Monitoring the residents of contaminated territories of the Russian Federation, Belarus and Ukraine .....	17
2.3.1 Evacuees .....	18
2.3.2 Residents of contaminated territories .....	18
2.4 Cross-cutting research issues .....	19
2.4.1 Integration of mental health and risks perception aspects .....	19
2.4.2 Dosimetry Research.....	20
2.4.3 Biological aspects .....	23
2.4.4 Potential expansion of the Chernobyl Tissue Bank.....	24
2.5 Co-operation aspects: the Chernobyl Research Committee.....	25
3 References .....	28
Annex.....	32

## LIST OF PARTICIPATING INSTITUTIONS

International Agency for Research on Cancer (IARC)

Association MELODI

Sateilyturvakeskus (STUK)

Bundesamt für Strahlenschutz (BfS)

State Institution Research Center for Radiation Medicine of the Academy of  
Medical Sciences of Ukraine (RCRM)

The Republican Research Center for Radiation Medicine and Human Ecology  
Institution (RRCRM & HE)

Medical Radiological Research Center – Russian Academy of Medical Sciences  
(MRRC)

United States Department of Health and Human Services (NCI)

## Executive Summary

In the period 2008 to 2010, an international group of experts and advisors under leadership of the International Agency for Research on Cancer (IARC) carried out the European Union funded project “ARCH: Agenda for Research on Chernobyl Health”. ARCH brought together a multidisciplinary group of experts with considerable experience in the follow-up of the health consequences of the accident. After conducting a comprehensive review of the current status of research on the health effects from the Chernobyl accident, the ARCH group proposed a Strategic Research Agenda (SRA) - [http://arch.iarc.fr/documents/ARCH\\_SRA.pdf](http://arch.iarc.fr/documents/ARCH_SRA.pdf) . The SRA underlined the need for well-designed and coordinated long-term studies. This view was shared by MELODI in its Advice of November 2011 ([http://melodi-online.eu/doc/NoteARCH\\_SRA.pdf](http://melodi-online.eu/doc/NoteARCH_SRA.pdf)). Following the ARCH SRA recommendations and the MELODI advice, the CO-CHER project (Cooperation on Chernobyl Health Research) funded by the European Union was established. The CO-CHER project partners are principally institutions that are extensively involved in conducting or supporting research on Chernobyl health effects. Representatives of the established international network of institutions and individual experts in epidemiology, clinical medicine, mental health, dosimetry, molecular biology, pathology and risk communication met in subgroups to discuss and agree upon the priorities in their field that comprise the current document. The group also carried out an assessment of the existing research infrastructures to form a basis for future research on long-term health effects of the Chernobyl.

**The goal of the agreed CO-CHER Chernobyl Research Programme is:**

- **to create an environment which ensures sustainable research and facilitates implementation of most informative studies of the responsible research institutes, including possible new collaborations and initiatives, and**
- **to outline a timetable for implementation of these activities.**

The populations exposed after the Chernobyl accident range: from the early liquidators (clean-up workers) with predominantly high levels of external radiation , to more than 500,000 of later liquidators with lower doses of mainly external irradiation from gamma-emitting radionuclides, and to the general population with predominantly internal irradiation from fallout and a very large variability of thyroid doses (e.g. from <0.05 Gy to 5 Gy) (UNSCEAR, 2008). Thyroid doses in pre-school children were 2-4 times higher than population average (UNSCEAR, 2008). Effective doses (excluding contribution to the thyroid) accumulated by most of the residents of the areas with <sup>137</sup>Cs deposition density >37 kBq/m<sup>2</sup> are much lower than thyroid doses (e.g. average cumulative effective dose was about 9 mSv over the 20 years following the accident, although about 150,000 people received more than 50 mSv over the same period) (UNSCEAR, 2008).

Chernobyl provides direct evidence of the consequences of a major nuclear accident; there is a need to turn this experience into an opportunity to fully understand radiation effects on human health in order to provide solid basis for radiation protection recommendations and to inform health planning for prevention and care for those exposed after future accidents. To capitalize fully from the Chernobyl experience there must be an appropriate research infrastructure.

In accordance with the ARCH SRA and the advice of the MELODI expert group, the highest priority defined by CO-CHER is the **establishment of a Chernobyl Lifespan cohort, similar to the action taken after the atomic bomb exposures in Japan, together with a series of individual studies covering the main health consequences.** The most suitable populations to form the Chernobyl Lifespan cohort as identified by the ARCH Expert group and further discussed within CO-CHER, are Chernobyl liquidators (clean-up workers), people who were exposed in childhood and had direct measurements of thyroid radioactivity performed shortly after the accident, and evacuees. Since the extensive efforts led by the US National Cancer Institute (NCI) in collaboration with research institutes in Belarus and Ukraine are already underway to combine data from people who were exposed in childhood and had thyroid radioactivity measurements, the large part of the current document focuses on the establishment of the Lifespan cohort of liquidators.

Continuing follow-up of Chernobyl-exposed populations should be instrumental in filling important gaps in current knowledge. Studies of the extensive thyroid gland exposure to radioactive iodine isotopes sustained as a result of the accident, particularly in childhood, can lead to a better understanding of the molecular mechanisms involved in thyroid carcinogenesis and thyroid cancer epidemics worldwide. Study populations with reliable dosimetry estimates and high-quality biological samples could provide information about the genomic signature of radiation-associated thyroid cancer, the correlation of phenotype/genotype and latency, iodine deficiency or radiation dose as well as about the existence of a genetic predisposition.

For cancers other than thyroid, where monitoring of cancer incidence rates indicate an increase, further assessment of phenotype and genotype characteristics, the magnitude of risk, as well as dose-response-relationships could also be informative. In addition, CO-CHER recommends assessment of the feasibility of integrating research on mental health and risk communication into well-established cohorts to assess the attributable health effects and assist in defining public health strategies and risk communication policies in the areas affected by the Chernobyl and Fukushima accidents, or any other potential future nuclear accidents.

CO-CHER recommends **a continuation of the project by convening a multinational body (Chernobyl Research Committee) to facilitate international collaborations and research. The group could be supported by a Secretariat to facilitate information exchange and provide guidance in obtaining and maintaining agreements between researchers and data custodians and to identify funding opportunities.** This would serve to support the scientific aspects of the Chernobyl Research Programme and its sustainable funding process and would supplement research that is already underway.

The proposed Chernobyl Research Programme recommends prioritized studies in the areas of epidemiology, biology, and dosimetry, defines their interrelationship and also covers management aspects. In this document we also describe other major existing collaborations between research institutions and commitments of funding organizations to avoid duplication of efforts and to indicate opportunities for added value through international cooperation. The current Research Programme covers a time period of up to 6 years and can be updated by the Chernobyl Research Committee, taking into account results of ongoing and completed research.

While specific topics of the Chernobyl Research Programme can be funded through various funding schemes, including open calls or research agreements between various institutions, the establishment

and maintenance of the Chernobyl Lifespan cohort, together with the Chernobyl Research Committee, shall be considered independently from these and supported through the agreements between the European Commission and relevant organisations in Belarus, the Russian Federation, Ukraine, the United States of America, and Japan.

# 1 Background

Following a comprehensive review of Chernobyl health research in 2010, the Agenda for Research on Chernobyl Health (ARCH) group of experts identified the most informative present and future studies of exposed populations and defined the scientific needs for improving the current understanding of the health consequences of the accident in their [Strategic Research Agenda](#) (SRA). The ARCH group of experts also defined future studies of high scientific, public health and societal importance which if funded could start shortly, within their [Project Proposals for Urgent Priorities](#). The Multidisciplinary European Low Dose Initiative (MELODI) expert group subsequently gave [advice](#) on the eligibility and feasibility (management, epidemiological, dosimetric, and biological aspects) of the proposed SRA and considered the main studies that should be supported.

Succeeding ARCH, the CO-CHER coordination action assembled a Scientific Expert Group comprised of representatives of the scientific institutions committed to long-term research on Chernobyl and of individual scientists with expertise in epidemiology, clinical medicine, dosimetry, molecular biology and pathology. The Scientific Expert Group further refined the Chernobyl research priorities based on the ARCH SRA with regard to the MELODI's advice and developed a Chernobyl Research Programme, together with a timetable for its implementation. After the CO-CHER kick-off meeting in Lyon in 2014, mental health and risk communication were defined as equally important areas for research as epidemiology, dosimetry and molecular biology and therefore should also be included in the potential research programme. To develop the Chernobyl Research Programme, each expert subgroup met to discuss and agree upon the priorities in their field. The prioritization was based on the relevance of the proposed research in terms of:

- answering key issues in the area of health risks following exposure to protracted low-dose radiation, as identified by the High Level Expert Group on European Low Dose Risk Research (HLEG 2009) and MELODI SRA;
- shaping public health policies in the three most affected countries;
- developing a long-term strategy for health surveillance of affected populations in the aftermath of nuclear accidents.

The Scientific Expert Group took into account the feasibility of the proposed research by closely interacting with CO-CHER Work package 3 whose task was to evaluate suitability of existing cohorts of exposed populations, dosimetry data bases and biobanks and the need for developing and/or improving research infrastructures necessary to conduct high-quality multidisciplinary studies.

The resulting proposed Chernobyl Research Programme was compiled by CO-CHER partners and representatives of the four expert subgroups and is based upon comprehensive reports and discussions.

## 2 Research priorities

### 2.1 Summary

The radioactive releases from the accident at the Chernobyl nuclear power plant in 1986 most heavily affected three European countries: Belarus, Ukraine, and the Russian Federation. Radioactive fallout from the accident was deposited all over the Northern Hemisphere and particularly Europe. It is assumed

that health consequences of the accident have occurred throughout Europe, but not necessarily at a level at which they could be detected by conducting epidemiological studies.

Presently, most of the knowledge about the effects of ionizing radiation comes from observations of Japanese atomic bomb survivors who were exposed to instantaneous high dose-rate external whole body radiation from the bombing of Hiroshima and Nagasaki (BEIR-V, 2005). Current risk estimates especially for internally incorporated radionuclides and for the mixture of external and internal radiation are very uncertain. Major questions remain about the magnitude of the risk of cancer and non-cancer diseases following exposure to low doses of ionizing radiation. It is particularly important to clarify important questions in radiation protection relating to the choice of models used to interpolate risk between populations with different background disease rates, for projection of risk over time, and for extrapolation of risk following primarily external high-dose and high dose-rate exposure to low-dose and low dose-rate exposures (BEIR-VII, 2006).

An improvement of our understanding of health risks from low-dose exposures and filling of existing gaps can most effectively be achieved by large, high-quality studies that integrate epidemiology, dosimetry, radiobiology and statistical modelling. Since events that contain a threat to health due to toxic exposures are very likely to give rise to long-term mental health effects (Havenaar, Cwikel, & Bromet, 2002), these outcomes should be studied as well. To make the best use of this unique opportunity to increase our understanding of effects of radiation and accidents, the CO-CHER project proposes the **Chernobyl Research Programme**, which is a sustainable plan for research into the health effects of the Chernobyl accident with optimal use of available resources. The success of such proposed future programme is highly dependent on collaboration between the researchers, data custodians, stakeholders and funding agencies that play a major role in assuring sustainability of Chernobyl research. The Chernobyl Research Programme presented here is based upon what is already known, what studies are ongoing or planned (for example, in exposed children) and on identified gaps in research. Based on this, recommendations are made for future studies, in particular amongst liquidators and possibly other affected populations. A Gantt chart summarizing the time frame, and the steps leading to future studies is shown in Annex.

The populations exposed after the Chernobyl accident range: from the early liquidators (clean-up workers), whose exposure was predominantly due to high levels of external radiation with whole body doses ranging from 0.8 to 16 Gy, to later liquidators (more than 500,000 people) who were exposed to lower doses of mainly external irradiation from gamma-emitting radionuclides with the mean external dose about 120 mGy (except a group of liquidators who were on site during the first weeks after the accident and whose thyroid dose were estimated to average 0.21 Gy), and to the general population whose exposure was predominantly due to internal radiation from fallout showing a very large variability of thyroid doses for all population groups (e.g. from less than 0.05 Gy to 5 Gy in evacuees (more than 100,000 people) and less than 50 mGy for most of non-evacuated residents of the contaminated territories in Belarus, the Russian Federation and Ukraine (UNSCEAR, 2008). Thyroid doses in pre-school children were 2-4 times higher than population average (UNSCEAR, 2008). Most of the residents of the areas with  $^{137}\text{Cs}$  deposition density more than 37 kBq/m<sup>2</sup> accumulated effective doses (excluding contributions to the thyroid) much lower than doses to the thyroid (e.g. average cumulative effective

dose was about 9 mSv in the first 20 years following the accident, however about 150,000 people (0.1% accumulated a dose more than 50 mSv over the same period) (UNSCEAR, 2008).

Epidemiological studies of populations affected by the Chernobyl accident have already provided important findings concerning the link between radiation and cancer (and non-cancer) outcomes. This has proved to be important for improving our scientific understanding of radiation effects and for the development of radiation protection measures in the case of future nuclear accidents. Nevertheless, many of the epidemiological studies on the radiation-related health effects of the Chernobyl accident suffer some methodological limitations (UN Chernobyl Forum "Health", 2006). The establishment of **the Chernobyl Lifespan Cohort** composed of populations most suitable for long-term research on the health effects of the Chernobyl accident is a key to successful implementation of the Chernobyl Research Programme and an important step to overcome the deficiencies and limitations of previous studies.

The most suitable populations for inclusion in the Chernobyl Lifespan cohort as identified by the ARCH Expert group and further discussed within CO-CHER, are described below. As efforts are already underway for combining data of those exposed in childhood and *in utero* coordinated by the US National Cancer Institute (NCI)), CO-CHER focuses on exploring the feasibility of constructing a Lifespan cohort of liquidators. The construction of the Lifespan cohort of liquidators will facilitate agreements for data sharing (similar to some ongoing projects, such as the Ukrainian-American thyroid cancer screening cohort (UkrAm) and the Chernobyl Tissue Bank (CTB)), while respecting the governance and ownership of the data for individual cohorts and developing robust mechanisms for protecting intellectual property rights (IPR). The Lifespan cohort of liquidators will be an important infrastructure for conducting future multidisciplinary studies on the health effects of low doses of radiation, integrating epidemiology, dosimetry, radiobiology and mental health. The cohort can add to other ongoing studies and infrastructures such as established biobanks, and methodological developments in the field of dosimetry. Priorities for research areas in each of the identified population groups are also discussed below, including ongoing research.

A mechanism to facilitate the collaboration and discuss ongoing and planned Chernobyl studies should be agreed upon and set up. **CO-CHER, therefore, recommends setting up a Chernobyl Research Committee that would discuss, prioritize and agree on the mechanisms for collaboration.** Inherent to such agreements is the need to take into account interests of the key institutions involved in Chernobyl research. CO-CHER also seeks to secure seed funding for convening the Chernobyl Research Committee and helping to launch new studies proposed in the Chernobyl Research Programme.

## 2.2 Populations suitable for long-term studies

### 2.2.1 Lifespan cohort of liquidators

Liquidators are clean-up workers from the former Soviet Union who were involved in the emergency response during the first days after the accident, as well as in the decontamination work, sarcophagus construction and recovery operation activities from 1986 to 1991. The highest level of external exposure occurred in 1986 and 1987. Doses received by liquidators varied considerably, with some early liquidators receiving doses up to a few Gy (UNSCEAR, 2011).

Cohorts of liquidators have already been established in the Russian Federation, Belarus, Ukraine, and in the Baltic countries (Estonia, Latvia and Lithuania). These cohorts comprise hundreds of thousands of

workers and offer a large potential for studying the health effects of protracted mainly external exposures with cumulative doses in the low and moderate dose range (around 100 mGy on average). Liquidators who worked close to the damaged reactor in the weeks following the accident also had the potential to receive substantial thyroid doses due to inhalation of radioactive iodine isotopes.

Up to 1991, information on 659,292 persons was recorded in the All-Union Distributed Clinico-Dosimetric Register maintained in Obninsk (UNSCEAR, 2011). After the dissolution of the Soviet Union, national Chernobyl registries continued independently in Belarus, the Russian Federation and Ukraine. The follow-up mechanisms of the national cohorts differ, although most of inclusion criteria overlap. Table 1 shows information on the potential size of each liquidators' cohort, including frequency and completeness of medical follow-up, numbers of diseased or migrated subjects and of those with official dose records (ODR).

**Table 1: Characteristics of existing cohorts of Chernobyl liquidators**

Country	Ukraine (UNSCEAR, 2008; Ostroumova et al., 2014)	Russian Federation (UNSCEAR, 2008)	Belarus (UNSCEAR, 2008)	Baltic Countries** (Rahu et al., 2013(a); 2013(b))
Total number	229,844	186,395	72,362	17,040 Latvia: 5,546 Estonia: 4,810 Lithuania: 6,684
Frequency and completeness (%) of medical follow-up	Annually 83-85%	Annually* 75-78%	Annually 97-99%	Latvia: annually Estonia: no programme Lithuania: no ongoing programme
% deceased	12% (31.12.2010)	20.5% (31.12.2010)	No data	Estonia: 21% (31.12.2009) Lithuania: 23% (31.12.2012)
% migrated	17% (31.12.2010)	No data	No data	Estonia: 12% (31.12.2009) Lithuania – 6% (31.12.2012)
Number of participants with official recorded dose	90,387	134,182	8,793	13,384
Mean external dose (mGy)	151	107	51	Estonia: 99 Latvia: 117 Lithuania: 109

\* Liquidators who participated in recovery operations after 1987 are screened biennially

\*\* Chernobyl registries do not exist but cohorts were established within the framework of the NCI study on cancer risk among Baltic Chernobyl clean-up workers (K. Rahu, Hakulinen, et al., 2013; M. Rahu et al., 2006; Tekkel et al., 1997)

In the Baltic countries, the passive follow-up for cancer incidence, migration and all-cause mortality is ensured through linkage with population-based cancer registries, and death and migration registries as a

part of research projects (Rahu et al., 2013b; 2014; 2015). It is not supported by national legislation or a continuous research programme. In Belarus and Ukraine, follow-up for cancer incidence and mortality can be accomplished through linkage with population-based national cancer registries (Hatch et al., 2015; Ostroumova et al., 2016), while in the Russian Federation, reporting of individual personalized information on new cancer cases and cause of death to the National Radiation and Epidemiological Registry is mandatory at the federal level (Kashcheev et al., 2015; 2016).

Up to now, studies on established cohorts of liquidators have provided some indications of possible links between radiation and cancer, as well as non-cancer diseases ((Prysyazhnyuk et al., 2007; Kesminiene et al., 2008; 2012; Zablotska et al., 2013; Rahu et al., 2013b; 2014; Ostroumova et al., 2014; Kashcheev et al., 2016). While some of the conducted studies were of a descriptive nature and therefore inconclusive due to limitations of study design and potential surveillance bias (Prysyazhnyuk et al., 2007; Ostroumova et al., 2014), other studies used to evaluate dose-response relationship using ODR of disputable quality (Chumak, 2007). Two case-control studies nested within the cohorts of liquidators from Ukraine (Zablotska et al., 2013), and Belarus, the Russian Federation and Baltic countries (Kesminiene et al., 2008) with individual doses reconstructed using the Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE) time and motion approach (Kryuchkov et al., 2009) indicated a dose-dependent excess for both other types of leukaemia than chronic lymphocytic leukaemia (CLL) and CLL. A case-control study nested within the cohorts of liquidators from Belarus, Russian Federation and Baltic countries found dose-response for thyroid cancer with both internal intake of radioiodines and external exposure (Kesminiene et al., 2012), which remained positive even after exclusion of tumours of diameter less than 1 cm which could have been detected due to the screening activities.

Another key finding in the screened cohort of Ukrainian liquidators funded and led by the U.S. Department of Energy (DOE) was an increased risk of cataracts with a dose threshold of not more than 0.7 Gy (Chumak et al., 2007; Worgul et al., 2007). The evidence of cardiovascular (CVD) diseases in liquidators is conflicting and the association with radiation exposure unclear due to the lack of validated dosimetry and information on other risk factors (e.g. smoking, alcohol consumption, diet and other lifestyle factors) that influence the development of CVD.

Careful analysis of the existing cohorts of liquidators within CO-CHER WP3 (Deliverable 3.1) has demonstrated that because of higher doses than the general population and established sources and procedures of cancer and non-cancer incident and mortality case ascertainment, they are suitable for the construction of a Lifespan cohort of liquidators.

As mentioned above, the official doses from the registries are problematic; case-control studies nested within cohorts offer therefore the most cost-efficient approach for estimating doses by means of reconstruction techniques and also the potential for determining possible confounders or effect modifiers. However, the individual dose reconstruction based on personal interviews is challenging 30 years after the accident and other possible improvements of individual dosimetric information in addition to the RADRUE method, e.g. validation of official doses, are discussed in detail elsewhere (Deliverable D3.2, Drozdovitch et al., 2016) and summarized in the dosimetry section below.

There are several small national collections of biological samples available from liquidators either assembled *ad hoc* or to investigate specific research hypotheses. For example, tissues are being collected from thyroid cancer cases in the cohort of Ukrainian liquidators. Sample collections are discussed in more detail in Deliverable 3.3. – Report on inventory of stored biological samples.

Combining cohorts of liquidators will increase statistical power to detect potential small health risks that cannot be adequately studied in individual cohorts. Combined data will provide a basis for designing and conducting epidemiological studies in the future (e.g. nested case-cohort or case-control studies).

To date, the available data suggest that priority shall be given to well-planned case-control studies of haematological malignancies (Zablotska et al., 2013; Kesminiene et al., 2008) and thyroid cancer (Kesminiene et al., 2012) nested in the combined cohort which could bring more certainty about the observed increase in risk of these malignancies among liquidators. For other solid cancers, analyses of cancer incidence data in the combined cohort could help to define further research priorities.

As there are national differences in registration procedures and follow-up mechanisms of liquidators, setting an oversight committee under the Chernobyl Research Committee, which can include data custodians and intellectual property right (IPR) owners will be an important priority. The committee will decide on the criteria for inclusion in the combined cohort, to agree upon and to harmonize the data to be combined, to develop and test procedures for combining and analysing joint data is recommended. The decision on the frequency of updating data sets from national cohorts for combined analyses shall be made by the Lifespan cohort oversight committee. The committee may also consider accepting and reviewing applications for specific analyses of combined data sets coming from researchers outside the institutions contributing the data to the Lifespan cohort of liquidators.

#### **The Chernobyl Research Programme identifies as priority areas:**

- 1. Construction of the Lifespan cohort of liquidators, possibly supported by the Lifespan cohort oversight committee and starting with a pilot phase that aims to:**
  - a. develop criteria and rules for inclusion in the combined cohort,**
  - b. agree upon and develop procedures for combining and analysing the data,**
  - c. set up protocols for assessment of individual dosimetry and biological sample collection, if possible.**
- 2. With the necessary agreements from those involved, the Lifespan cohort could be used to investigate risks and their temporal patterns of solid cancers, leukaemia, cardiovascular diseases and mental health outcomes associated with exposure due to the Chernobyl accident.**

#### **2.2.2 Ongoing studies of exposed children with thyroid activity measurements after the accident**

There is already a major ongoing effort jointly led by the US National Cancer Institute (NCI), Institute of Endocrinology and Metabolism (IEM) in Ukraine and Republican Research Centre for Radiation Medicine and Human Ecology (RRCRM&HE) in Belarus to combine data from the major populations exposed in childhood. Their past and ongoing efforts are summarized here.

In the 1990s, two general population cohorts were established in Belarus (the BelAm cohort) and Ukraine (the UkrAm cohort) with scientific leadership of US NCI and financial support from the US DOE and NCI, based on a roster of all individuals aged 18 or younger at the time of the accident who lived in the most contaminated regions of these countries and whose thyroid activity was measured within two months of the accident (Stezhko et al., 2004). The cohorts, which include about 25,000 subjects from Belarus and Ukraine, have been periodically screened for thyroid disease with ultrasound examination

and palpation since 1998 (see Table 2) and have provided valuable information on thyroid cancer and thyroid disease risk. The cohorts continue to be followed up and studied in several NCI-supported research projects (Stezhko et al., 2004; Zablotska et al., 2010; Brenner et al., 2011).

**Table 2: Characteristics of exposed children with direct thyroid activity measurement**

Country	Ukraine (Likhtarov et al., 2014)	Belarus (Drozdovitch et al., 2013; 2015)	Russian Federation (UNSCEAR, 2010)
Total with thyroid activity measurements	75,349	39,188	47,949
Included in screening cohort	13,243	11,918	None
Total with reconstructed individual doses	13,204	11,732	2,457*
Mean thyroid dose (max), Gy	0.65 (42)	0.68 (39)	0.13 (5.9)*
Whole body dose, Gy	NA	0.013	NA

\* Subjects who were under the age of 10 years at the time of the accident. NA = not available

Efforts to combine the Ukrainian and Belarussian cohorts are already underway led by NCI, IEM and RRCRM&HE. The studies of Ukraine and Belarus are compatible in terms of methods for cohort construction, follow-up and screening protocol and procedures; the ultrasound screening methods used within the Russian cohort have to be checked for its comparability with both cohorts established by the NCI. The UkrAm and BelAm cohorts provide unique opportunities to explore interactions between genetic factors and radiation, identify markers of radiation induced thyroid cancer and derive characteristics of radiation risks. These studies comprise individual thyroid dose measurements, regular screening cycles (the frequency of cycles is different between UkrAm and BelAm (Stezhko et al., 2004; Zablotska et al., 2010; Brenner et al., 2011)), and samples of thyroid cancer tissue (from UkrAm only) archived in the CTB. NCI is currently leading a major study in collaboration with IEM and CTB to search for potential radiation signatures using whole genome sequencing in the well-characterized thyroid tissue samples from the Ukraine.

#### **The Chernobyl Research Programme:**

- 1. Emphasises as priority area follow-up and possible pooling of the UkrAm and BelAm cohorts.**
- 2. Recommends strengthening the radiobiological research and expanding biological specimen collections from the UkrAm and BelAm cohorts.**
- 3. In addition to the thyroid cancer specimens stored at CTB from the UkrAm and in Belarus from BelAm cohort members, collection of other samples may be considered if clearly linked to the exposure from the Chernobyl accident. This will support risk analyses and the identification of potential markers of radiation induced tumours.**

A cohort of nearly 50,000 individuals of the most contaminated regions in the Russian Federation, whose individual thyroid doses were measured from May to June 1986 by the Medical Radiological Research Centre (MRRC) in the Kaluga region and by the Laboratory of Clinical Dosimetry of Bryansk Oncology Dispensary in the Bryansk region (Zvonova, Balonov, Bratilova, 1998) is included in the Russian National Radiation Epidemiological Registry. About 70% of those with the reconstructed thyroid doses have been followed through the regular medical check-up programme. While the studies of Ukraine and Belarus are compatible in terms of methods for cohort construction, follow-up and screening protocol and procedures; the methodology of screening and dose reconstruction within the Russian cohort has to be investigated before any recommendations for considering this cohort for further studies can be made.

### 2.2.3 Ongoing research of those exposed *in utero*

A small cohort was established by NCI, initially to study the risk of thyroid disease for children exposed *in utero* in Ukraine; the cohort continues to be followed for this and other outcomes (Hatch et al., 2009). This cohort consists of mother-child pairs (children born during the period 26 April 1986 – 31 March 1987.) The mothers were identified from linkage of the records of the thyroid activity measurements database at the National Research Centre for Radiation Medicine (NRCRM) with birth records at the Institute of Paediatrics, Obstetrics and Gynaecology in Kyiv, Ukraine. Individual I-131 thyroid doses were estimated for all study participants. The cohort was first screened for thyroid diseases in 2003-2006; a 2<sup>nd</sup> screening of the cohort has just been completed recently.

In Belarus, a cohort of *in-utero* exposed subjects is now under construction under leadership of NCI, in collaboration with RRCRM&HE. The study is jointly funded by NCI and the National Institute of Allergy and Infectious Diseases (NIAID). For an overview of both cohorts see Table 3, for more details - Deliverable 3.1 “Evaluation of the cohorts of exposed populations suitable to form Chernobyl Lifespan cohorts”.

**Table 3: Characteristics of exposed *in utero* cohorts**

Country	Ukraine (Hatch et al., 2009; Likhtarov et al., 2011)	Belarus (Yauseyenka et al., 2016) *
Total (mother-child pairs)	2,582	2,500 – 3,000
Number of mothers with direct thyroid measurements	720	400-500 <sup>#</sup>
Mean thyroid dose. mGy	72 2.1 (1 <sup>st</sup> Trimester) 131 (3 <sup>rd</sup> Trimester)	Work in progress

\* The cohort is currently under construction

<sup>#</sup> As the cohort is currently under construction, the number of subjects whose mothers had direct thyroid activity measurements is preliminary and could change in the future

NCI, Ukrainian and Belarusian investigators will explore the feasibility of combining the two *in utero* cohorts once construction of the Belarussian cohort is completed.

The Chernobyl Research Programme considers that, although the numbers of exposed *in utero* are small, due to the uniqueness of this particular population the ongoing efforts of NCI and research institutes in Belarus and Ukraine are priority area, particularly for the evaluation of:

1. The effects of foetal thyroid exposure and
2. Neurobehavioral and cognitive performance.

#### 2.2.4 Feasibility of setting up a cohort of offspring of liquidators and evacuees

The total number of children born to exposed parents, including liquidators, in national Chernobyl registries is about 500,000, with the largest number of registered offspring in Ukraine (428,045). Given the level of exposures (including to gonads) received by liquidators and evacuees, studies of their offspring are potentially suitable for detecting effects of parental exposure, although previous studies on these effects are limited and in some cases have given conflicting results (Weinberg et al., 2001; Aghajanyan et al., 2011; Fucic et al., 2016).

The NCI, in collaboration with NRCRM, Ukraine, is currently conducting a study on comprehensive characterization of genomic alterations and inherited variation patterns in offspring associated with parental pre-conception exposure to radiation from the Chernobyl accident. The level of effort invested at the moment is sufficient, and the results of this study should be assessed before deciding how to prioritize further research in this population.

In the Baltic countries, it is feasible to link available data on offspring of liquidators with cancer and other population registries.

**The Chernobyl Research Programme recommends:**

1. To follow upon the results of the study currently in progress at the NCI to make a decision about further prioritization of research on pre-conceptional exposure effects in offspring;
2. Depending on the outcome of the NCI - NRCRM study, a feasibility study to evaluate potential size of the offspring cohort, quality of follow-up, traceability (particularly offspring of evacuees) – to validate the registry-based information, exposure levels and possibility of obtaining biological specimens from parents and their offspring, maybe considered in the future.

#### 2.3 Monitoring the residents of contaminated territories of the Russian Federation, Belarus and Ukraine

Affected persons of the general population comprise evacuees who were relocated from radioactively contaminated areas (>37 kBq/m<sup>2</sup>) and persons who continued to live in areas of Belarus, Ukraine and the Russian Federation with lower contamination levels (Cardis et al., 2006). Compared to the dose to the thyroid from exposure to radioactive iodine isotopes, in particular I-131, external irradiation and ingestion of long-lived caesium (Cs) isotopes resulted in significantly lower whole-body doses to the general population, even in residents of highly contaminated areas with Cs-137 deposition density more than 1,480 kBq/m<sup>2</sup> (up to 120 mSv for 1986-2005) or in evacuees (around 35 mSv) (UNSCEAR, 2011).

### 2.3.1 Evacuees

In the days after the Chernobyl accident, about 115,000 residents living within the 30 km exclusion zone were evacuated and a further 220,000 residents of contaminated territories were relocated in the following months (UNSCEAR, 2011). According to the *in vivo* measurements, the mean contribution of very short lived radioiodines and telluriums to total thyroid dose was 30% in evacuees from Pripjat who did not take stable iodide and were evacuated within 40 h after the accident (Balonov et al., 2003). For the residents of Pripjat, who were evacuated 40 hours after the accident, the population-weighted average thyroid dose is estimated to range from 275 mGy in adults to about 1,000 mGy in preschool children (UNSCEAR, 2011). Much higher doses are estimated for the Belarussian population evacuated in May 1986 - about 920 mGy in adults and 4,600 mGy in preschool children (UNSCEAR 2011). Table 4 shows the size of the population that was evacuated and resides in radioactively contaminated areas of the three most affected countries.

**Table 4: Characteristics of evacuees and residents of contaminated territories (UNSCEAR 2008)**

Country	Ukraine	Belarus	Russian Federation
Total number of evacuees	89,600	24,725	9,944
Number of evacuees registered in Chernobyl State Registry	49,887	5,951	7,508
Residents of radioactively contaminated areas	1,554,269	1,513,826	443,021

The size of the evacuee populations and substantial exposure levels to the thyroid make them of interest for health follow-up and research. Many of them were lost to follow-up but those who are registered in the Chernobyl registries enable reconstructing rosters of these populations.

#### The Chernobyl Research Programme recommends:

- **To assess completeness, representativeness and quality of follow-up of evacuees registered in the state Chernobyl registries in order to evaluate their suitability for the lifespan follow-up.**

If feasibility is proven, studies of the evacuees in the roster could be informative for evaluating risks of thyroid cancer and non-cancer thyroid diseases as well as the joint effects of evacuation and radiation, on cardiovascular and cerebrovascular diseases, and mental health.

### 2.3.2 Residents of contaminated territories

It is expected that monitoring of cancer incidence (except thyroid carcinoma) within the population residing in contaminated territories will provide little information, because the radiation dose outside the thyroid gland in the general population was comparably low. Between 1986 and 2005, the average additional radiation exposure was estimated to be 9 mSv compared to natural background radiation of

50 mSv within this period and because the observed increases in cancer incidence can be due to other factors, including the improvement of cancer registration (Cardis et al., 2006).

Nevertheless, methodological support and provision of training for staff of cancer registries in Belarus, Ukraine and the contaminated regions of the Russian Federation could help standardise follow-up and monitoring of cancer incidence trends in populations residing in contaminated areas in order to assist public health planning and identify increases that could be further investigated through analytical epidemiological studies, if justified.

**Therefore, the Chernobyl Research Programme recommends:**

- 1. Methodologically sound studies of cancer incidence and dose at the small administrative unit (such as rayon) level that can provide indications for conducting further analytical studies, enabling reconstruction of individual doses and control for other risk factors.**
- 2. Continuous and accurate monitoring of overall and site-specific cancer incidence in the affected areas, particularly in those exposed early in life that could be important for public health purposes.**

The retrospective evaluation of leukaemia incidence and mortality trends among those who were exposed *in utero* and/or in childhood through existing cancer registries (e.g. childhood cancer registries that participated in European childhood leukaemia study – inside and outside the three most affected countries) should be one of the priority areas, as well as monitoring breast cancer incidence trends (considering conducting a population-based case-control study of breast cancer as the next step).

## 2.4 Cross-cutting research issues

### 2.4.1 Integration of mental health and risks perception aspects

The population affected by the Chernobyl accident was confronted with a plurality of stressors, comprising late and chaotic evacuation, stigmatization or resentment of the non-affected population (Bromet, 2012). Independent of radiation exposure, the affected population showed higher prevalence of depression, anxiety, post-traumatic stress-disorder or psychosomatic symptoms as compared to unexposed (Bromet, 2014; Bromet, Havenaar, Guey, 2011). In addition to the somatic health effects, the impairment of the mental health of liquidators was one of the most profound consequences of the Chernobyl accident (Bromet, Havenaar, Guey, 2011; Laidra et al., 2015; Loganovsky et al., 2008; Rahu et al., 2008).

In 2011, three high priority groups were identified for research on mental health consequences of Chernobyl: liquidators, children exposed *in utero* or as infants, and adult populations with various levels of exposure (Bromet, Havenaar, Guey, 2011).

However, the assessment of mental health in case of the Chernobyl accident is difficult as studies carried out in regions that are susceptible to socio-economic instability are prone to influences that complicate interpretation of results. Furthermore, up to now, mental health studies have often been limited by methodological problems, as they often did not consider other important risk factors (e.g. age, alcohol consumption) or did not use relevant and internationally meaningful measures of both exposure and of

mental health status. There are multiple challenges inherent in developing strategies for understanding the long-term physical and mental health of affected populations. These challenges may be due to the specific cultural, demographic and political contexts in which they occur, the varying degrees of physical, social and psychological trauma, and the varying levels of contamination that can make it impossible to establish individualized exposomes (Bromet, Luft, 2015).

Translationally useful research questions are often best addressed with longitudinal data. In this respect, monitoring program samples, especially programs with high retention rates, are immensely valuable. With appropriate consent, data collected routinely by the program can be combined with mental health study materials. Existing cohorts of liquidators, particularly in the Baltic countries, or children with thyroid activity measurements could be used to integrate elements of mental health assessment.

To date most of Chernobyl studies have focussed on specific diseases, leaving the extent and pathogenesis of multisystem disorders and symptoms poorly understood. Some studies have administered in-depth measures of mental health along with brief self-reports about physical health, or in-depth examinations of physical health with limited to no information on mental health, but not both. Given the multimorbidity of health and mental health (Atun, 2010), it is critical that studies of liquidators and exposed residents include state-of-the-art measures of both aspects of health. This also hinders the design of multidisciplinary, maximally efficacious, intervention programs (Bromet, Luft, 2015).

Another unique challenge for studies of populations affected by massive disasters is the loss of trust in scientists (Bromet, Luft, 2015). To a large extent, this is a consequence of the political issues surrounding responsibility for the cause and remediation of the disaster, media reports on health effects that conflict with scientific findings, and a lack of experience among scientists in communicating science to the general public. Studies on risk perception, despite that 30 years after the accident they can be affected by recall bias, can help to inform risk communication strategies in case of future accidents.

The long-term mental health effects and major concerns of the affected population (evacuees, liquidators, exposed early in life, thyroidectomy patients, residents of contaminated areas, resettlers and offspring of these) were not adequately evaluated.

**The Chernobyl Research Programme recommends:**

- 1. To initiate integration of mental health specialists into multidisciplinary teams of ongoing or planned studies on physical health effects.**
- 2. To integrate elements of mental health assessment in the ongoing or planned epidemiological studies of liquidators and exposed residents to identify consistent patterns of long-term health effects that can be used for developing and tailoring intervention programs in the aftermath of nuclear disasters.**

#### 2.4.2 Dosimetry Research

Dosimetry is essential for all radiation effect studies. The general strategy to support dose estimation for analytical epidemiological studies after a nuclear reactor accident includes, among others: collection of as many individual-based radiation measurements as possible for subjects in the target population; collection of personal and lifestyle information, and information on the spatial and temporal patterns in the radiation field; validation of the dose estimates by independent measurements or strategies; and

qualitative and quantitative evaluation of the uncertainties associated with dose estimates (Bouville et al., 2014).

Most of the Chernobyl-related analytical studies assessed risk of thyroid cancer and other thyroid diseases. Therefore, the major efforts were invested on estimation of thyroid doses and their uncertainties. Direct thyroid measurements are considered as most reliable prerequisite for dose assessment, despite their own uncertainties. However, not every individual residing in contaminated regions of Belarus, Ukraine and the Russian Federation had their thyroid radioactivity measured after the accident, including the subjects enrolled in epidemiological studies. Only two cohort studies have individual-based radiation measurements available for all cohort members and provide an evaluation of uncertainties in the calculated doses. These cohort studies of individuals exposed as children and adolescents at the time of the Chernobyl accident are carried out in Belarus (BelAm), by the Republican Research Centre for Radiation Medicine and Human Ecology (Gomel), and in Ukraine (UkrAm), by the Institute of Endocrinology and Metabolism (Kyiv), in close collaboration with, and funded by, the US NCI (Likhtarov et al., 2014; Drozdovitch et al., 2013). A unified study protocol and dose estimation approach were used in both studies.

Methods for individual thyroid dose reconstruction were developed and individual doses estimated for all individuals included in the case-control study of thyroid cancer risk in young people from Belarus and the Russian Federation (Drozdovitch et al., 2010; Stepanenko et al., 2004). For majority of study participants, thyroid radioactivity measurements were unavailable but validity of modelled thyroid doses was confirmed through comparison with instrumental doses available either for limited number of individuals included in the study or coming from the same area. The uncertainty in the individual thyroid doses was estimated using Monte-Carlo calculation procedure accounting for both shared and unshared errors (Drozdovitch et al., 2015). There is still a need for a thorough comparison between the thyroid doses based on thyroid activity measurements and doses calculated with ecological model providing the variation of the thyroid activities before and after measurement. It would help to improve the accuracy of ecological models used to predict thyroid doses in epidemiologic studies with a limited number or no thyroid activity measurements.

For other organ doses than thyroid, there are two major contributors: (1) external irradiation, resulting from a radionuclide mix and (2) internal irradiation, resulting essentially from intake of  $^{134}\text{Cs}$  and  $^{137}\text{Cs}$ . For external irradiation, there are two areas that need further investigation i.e. the estimation of the doses received in cities, where radionuclides are thought have been removed more efficiently than in rural areas and where buildings provided more effective shielding; (2) the estimation of the long-term variation of the vertical migration of  $^{137}\text{Cs}$  in soils of rural areas. For internal contamination from  $^{134}\text{Cs}$  and  $^{137}\text{Cs}$ , it would be useful to develop an ecological model consistent with the available whole-body measurements and Cs concentration in milk.

The RADRUE method was developed and extensively tested by an international group of experts coordinated by IARC for studies of Chernobyl liquidators (Kryuchkov et al., 2009). The method was applied to reconstruct doses to the red bone marrow and thyroid from external radiation in nested case-control studies of liquidators (Kesminiene et al., 2007; 2012; Zablotska et al., 2013). The rationale behind the RADRUE technique is very straightforward: it is based on the calculation of external dose as a product of the exposure rate and irradiation time with shielding taken into account. In order to evaluate

the intrinsic uncertainties, a Monte-Carlo procedure was used to calculate 10,000 individual stochastic dose estimates for each study subject. The validity testing involved various exercises of inter-comparison between the RADRUE doses and other most reliable dose estimates available for different groups of liquidators (Kryuchkov et al., 2009).

Nevertheless, weaknesses of the RADRUE method include: (1) it is labour intensive and costly, and (2) the uncertainties in the resulting dose estimates could be quite large, because the essential input data are obtained by means of personal interviews, that may be unreliable and are very difficult to evaluate. For larger cohort studies, a thorough analysis of the ODRs and available daily dose rates measured around the Chernobyl NPP site could help to determine if and when the ODRs could be used instead of the RADRUE dose estimation for individuals and groups of workers.

Other dosimetry methods, particularly biodosimetry (e.g. stable and unstable chromosome aberrations, electron paramagnetic resonance), are only available for a limited number of liquidators; they were primarily used to validate the dose estimates (Chumak et al., 2005), which, for the main analytical studies, were obtained using the RADRUE method described above. In the future, efforts to validate the ODRs by means of a comparison with the results of currently available EPR and FISH measurements and to perform more EPR and FISH measurements, if they appear to be justified, should be made.

It is noted that many uncertainties in the parameter values that are used to calculate doses for Chernobyl studies are ignored and/or based on expert judgments that are not always justified. There is clearly a need to develop guidelines for evaluation of uncertainty in doses (including shared and unshared errors). Since the reconstruction of individual doses often depend on the quality of subject's answers to the questionnaire about individual behaviour 30 years ago, development of a method to validate questionnaire responses and evaluate related uncertainties is also very important.

A careful review of dose reconstruction methods applied in Chernobyl related epidemiological studies was carried out within CO-CHER WP3 (more details in Deliverable 3.2). It was recognized that it is of primary importance to conduct more thorough inventory of the existing dosimetry data that were collected in the three most affected countries, especially in the first few months after the accident, to evaluate their potential and accessibility for the improvement of the current dose estimates.

#### **The Chernobyl Research Programme recommends:**

- 1. For reconstructing doses to the residents of contaminated areas:**
  - a) to carry on further improvement of ecological models to predict thyroid doses for epidemiologic studies with a limited number or no thyroid activity measurements.**
  - b) to consider all available sources for improving precision of input parameters for reconstructing other organ than thyroid doses from internal and external exposures**
- 2. For studies on Chernobyl liquidators:**
  - a) to perform analysis and validation of the official dose records (ODR), including comparison with available EPR and FISH measurements (for calculating doses from external exposures).**
  - b) to analyse the direct thyroid measurements available for a sample of liquidators in order to improve the model to calculate thyroid doses for the early liquidators.**

### **3. To develop guidelines for evaluation of uncertainty in doses (including shared and unshared errors).**

#### 2.4.3 Biological aspects

A great deal has been already learned about mechanisms of radiation-linked thyroid carcinogenesis from the studies of populations exposed after the Chernobyl accident. However, the CO-CHER Expert group noted limitations in some of these studies:

- Aside from the systematic and integrated approaches that are employed by CTB for collecting tumour and blood samples, including samples from the UkrAm cohort, *ad hoc* approaches have been employed in most of other studies;
- Molecular studies have seldom been linked to epidemiological studies.

Systematic studies may inform not only the molecular mechanisms of thyroid neoplasia with the potential for elucidating the reasons for sporadic thyroid cancer epidemics worldwide but also of non-thyroid neoplasia and non-neoplastic diseases. Furthermore, they can provide a basis for thyroid screening following nuclear accidents and optimize monitoring strategies for thyroid lesions in a general population.

As described above, important molecular and morphological studies of thyroid cancer are ongoing in the cohorts of exposed children with good dosimetry (including BelAm and UkrAm cohorts, CTB cases). These studies aim to identify a possible genomic signature of radiation-associated thyroid cancer; to find potential phenotype and genotype correlation with latency, iodine deficiency, radiation dose, and exposure *in utero*; to assess the genetic predisposition, and to define molecular mechanisms promoting thyroid carcinogenesis.

While most of the studies concentrated on thyroid cancer and non-cancer diseases, molecular studies of non-thyroid cancers are limited or non-existent. There is an ongoing study carried out by Fred Hutchinson Cancer Research Centre (FHCRC), USA, on premenopausal breast cancer risk related to individual breast radiation dose from the Chernobyl accident in female residents of Bryansk Oblast, Russia. The study also aims at investigating whether the association of breast cancer risk with radiation exposure differs according to characteristics of breast cancer, including hormone receptor status, genomic loss and gain, and specific alterations in 14 selected DNA repair genes. Fresh breast tumour tissue and blood samples are being collected. The study results are not yet available; however it would help to decide about further prioritisation of non-thyroid cancer molecular studies. The ongoing study is well in line with the conclusions of Pukkala et al., 2006 that further studies investigating the role of host and environmental factors are desirable to better understand the increased risk in breast cancer found in young women in the most contaminated districts of Belarus and Ukraine.

#### **It is recommended:**

- 1. To follow-up temporal trends of thyroid cancer incidence in the population of contaminated areas through population-based cancer registries and to link those cancer registries to detailed information on pathological types and sub-types, and tumour size.**

2. **To investigate if the phenotype and genotype of thyroid cancer in persons exposed in adulthood are similar to those observed in exposed in childhood (e.g., in the studies of thyroid cancer among liquidators).**
3. **Studies of molecular features of other cancers than thyroid (e.g. premenopausal breast cancer in women exposed at young age, puberty, or during lactation, brain tumours and haematological malignancies in clean-up workers) could also help to establish a link between the increase in incidence (if observed) and radiation exposure.**
4. **Pilot studies shall ascertain if collection of blood and tumour tissue can be integrated in the Lifespan cohort.**

#### 2.4.4 Potential expansion of the Chernobyl Tissue Bank

The Chernobyl Tissue Bank (CTB) illustrates the feasibility of a combined sustainable support process (Thomas et al., 2012). Its establishment was made possible through a combined financial support from the US NCI, the European Commission, and the Sasakawa Memorial Health Foundation (SMHF), with collaborations and participations from the governments of the Ukraine and the Russian Federation.

The CTB is the first international cooperation that seeks to establish a collection of biological samples from tumours and normal tissues from patients for whom the aetiology of thyroid cancer is known - exposure to radioiodine in childhood. The project is currently jointly funded by the NCI and the SMHF. The project is coordinated from Imperial College, London and together with Institutes in the Russian Federation (the Medical Radiological Research Centre in Obninsk) and Ukraine (the Institute of Endocrinology and Metabolism in Kiev) to support local scientists and clinicians to manage specimen collections from thyroid cancer patients following exposure to radiation from the Chernobyl accident. Belarus was initially included in the project, but is currently suspended from the CTB. The project has the full support of the governments of the Russian Federation and Ukraine.

The major CTB goal is to provide a research resource for both ongoing and future studies on the health consequences of the Chernobyl accident. It seeks to maximize the amount of information obtained from the collected tissue samples by providing multiple aliquots of RNA and DNA extracted from well-documented pathological specimens to a number of researchers world-wide and to conserve this valuable material for future generations of scientists. It exists to promote collaborative, rather than competitive, research on a limited biological resource.

To date, the review of other existing biological samples within the CO-CHER project showed that there are further usable collections of biological samples. Within a NCI-funded collaborative project for measurements of radiation doses using biomarkers, STUK has stored about 3,000 biological samples constituting of cell suspensions (primary lymphocytes) from a cohort of male liquidators aged 18 to 63 at time of the accident and who worked at Chernobyl from 1986 to 1987. The majority of those liquidators came from Baltic countries, mainly Estonia and received doses from 1 to 350 mGy. Complete health follow up data to match the samples can be obtained from Estonia.

There is a large collection of thyroid tumour tissues, blood and DNA from thyroid cancer patients in Belarus, currently stored at the premises of the Belarusian Medical Academy of Post-graduate Education and partially being moved to the National Cancer Centre (NCC) of Belarus. The contents and quality of

this biomaterial needs to be evaluated and discussions are ongoing between IARC, NCI and the Belarussian partners concerning the possible access to the samples for conducting inventory and quality check.

Apart from these collections, the review within the CO-CHER project also revealed that smaller collections of *ad hoc* collected samples are stored but their further in-depth investigation need more time and resources to evaluate if they could be linked to individual information (including ethics considerations).

Based on the results of the CO-CHER project inventory on existing tissue banks, the **Chernobyl Research Programme recommends:**

- 1. Collaboration between the CTB and investigators in charge of the collections of biological samples, keeping in mind that such collections may not have employed a systematic approach.**
- 2. Collection of samples for individuals for whom precise dose estimates are available.**

Within the expansion of follow-up of the liquidator cohorts, a large-scale tissue bank for members of these cohorts may be considered if available resources cannot fulfil this need.

## 2.5 Co-operation aspects: the Chernobyl Research Committee

It is important to carry out research that will ultimately provide a comprehensive picture of the health consequences of the largest nuclear accident in the world to date. Political perspectives are important in the collaboration with and between the three countries most affected by the Chernobyl accident, and therefore it is essential that sustainable agreements with the relevant authorities from Belarus, the Russian Federation and Ukraine as well as with research institutions are obtained and maintained.

Maintaining and continuing the most informative cohorts that have been already set up in individual countries may require a combined effort of the international research community to maximise the scientific output and to guarantee the sustainability. Standardization of health indicators, harmonization of the methodology used, quality control, data validation, facilitation of obtaining and maintaining various agreements (with national ethics committees, authorities, international partners) could be encouraged by an international scientific oversight body.

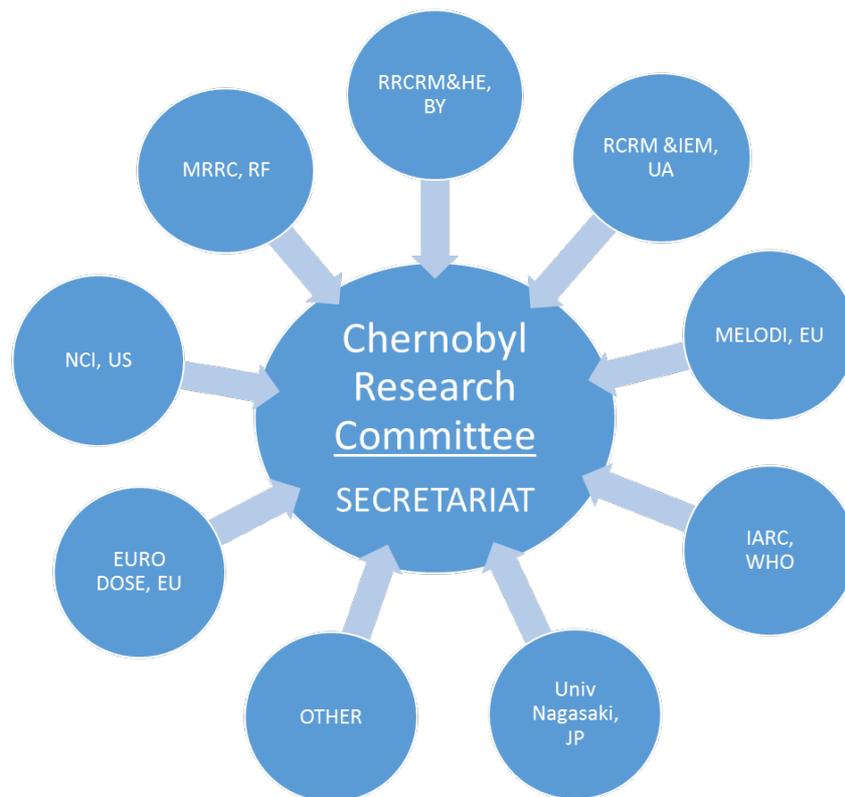
**CO-CHER, therefore, aims to agree on the mechanism for collaboration and recommends setting up a Chernobyl Research Committee.** Inherent to such agreement, is the need to take into account interests of the key institutions involved in Chernobyl research. CO-CHER also seeks to secure seed funding for convening the Chernobyl Research Committee and helping to launch new studies proposed in the Chernobyl Research Programme.

**The Chernobyl Research Committee should comprise representatives of the main research and funding institutions that are committed to sustainable research of the health effects of the Chernobyl accident which have been identified through consultations with the institutes involved in the CO-CHER network and is open to other institutions that are extensively involved in research on Chernobyl health effects (Figure).**

**The role of the Chernobyl Research Committee includes (but is not limited to):**

- Making strategic decisions on combining efforts to ensure sustainability of main infrastructures, such as Chernobyl Lifespan cohort(s);
- Serving as a platform for scientific information exchange;
- Creating environment for obtaining and maintaining agreements between researchers and data custodians;
- Enabling future pooling or meta-analyses of data from previously conducted individual studies (provided there is agreement of the data custodians and IPR holders).

Figure: Chernobyl Research Committee structure



The Chernobyl Research Committee will be supported by a Secretariat in practical matters. IARC has coordinated the ARCH and CO-CHER initiatives. However, the location and composition of the future Secretariat is to be decided by the Chernobyl Research Committee members. The role of the Secretariat includes: maintaining regular contact and communication within the Chernobyl Research Committee; documenting and archiving decisions by the Committee; organising meetings and preparing their minutes; running the joint Chernobyl research website; acting as the information interface between the various research activities and the Research Committee. The Secretariat could also facilitate contacts between researchers and pertinent ethics committees for continuation/ setting up of multidisciplinary studies, and identifying and disseminating information on funding opportunities. It also could assist in obtaining agreements regarding the collection and/or accessing of existing biological samples. The

Secretariat will provide guidance in obtaining and maintaining agreements between researchers and data custodians and to identify funding opportunities.

It is recommended to establish small oversight committees for setting up (where necessary) the lifespan cohorts to facilitate reaching agreements on the data to be combined. The Secretariat will transmit their reports to the Research Committee to ensure synergies are used within the Chernobyl research strategy and to ensure everyone is aware of the latest developments.

The Secretariat will provide methodological support and training for staff of cancer registries to follow up populations and monitor cancer incidence trends for public health planning purposes and for the detection of increases that should be further investigated through analytical epidemiological studies.

Setting up the mechanism for convening the Chernobyl Research Committee and supporting Secretariat will require immediate funding. Finalizing the sustainable funding agreement could take considerable time and cost, and it is important to identify seed funding (for the first 1-2 years) through consultations and agreements with potential funding bodies that already have been initiated by CO-CHER.

### 3 References

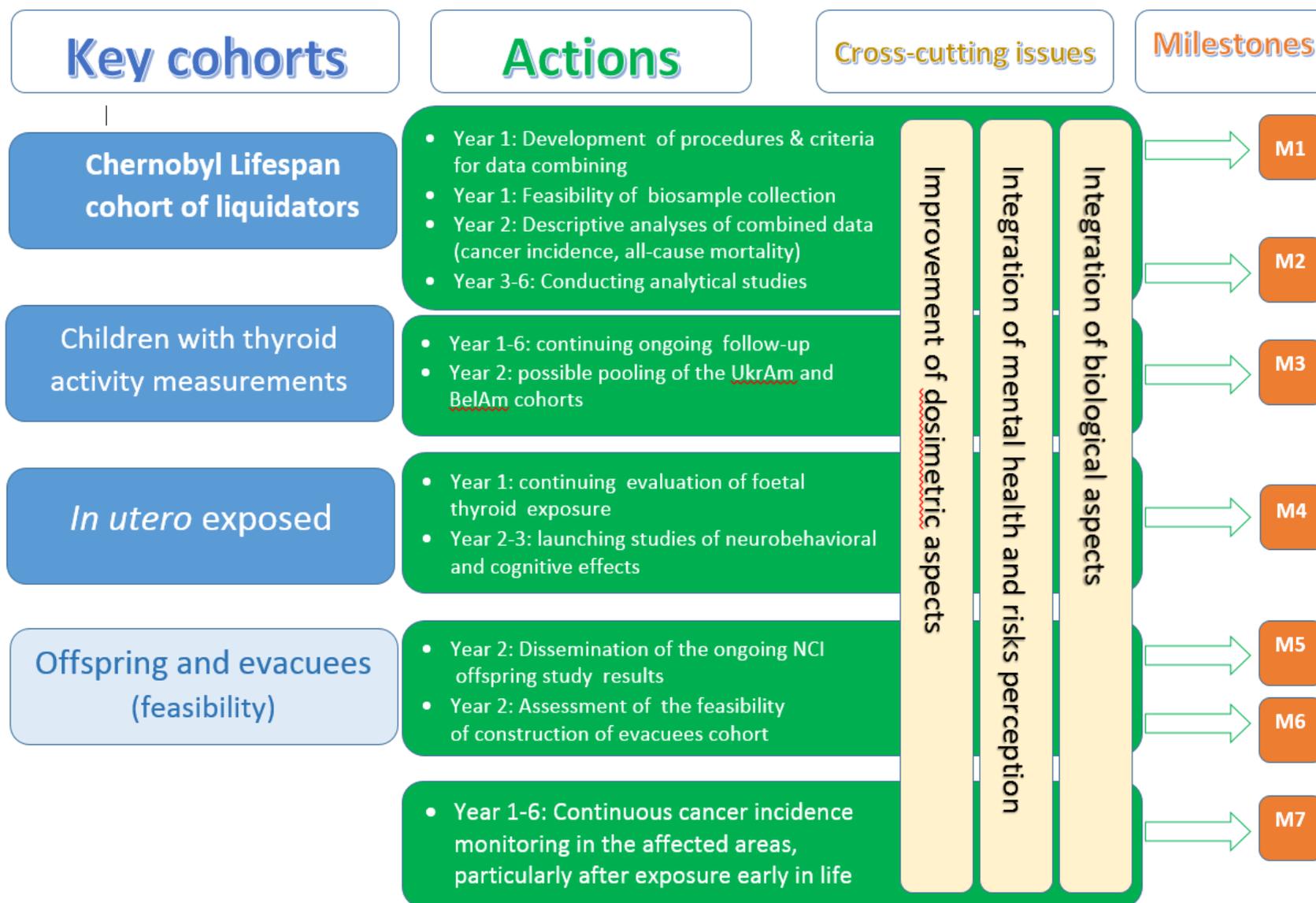
- Aghajanyan A, Kuzmina N, Sipyagyna A, Baleva L, Suskov I. (2011) Analysis of genomic instability in the offspring of fathers exposed to low doses of ionizing radiation. *Environ Mol Mutagen* 52(7):538-46.
- Atun R (2015) Transitioning health systems for multimorbidity. *Lancet* 386(9995): 721–722
- Balonov M, Kaidanovsky G, Zvonova I, et al. (2003) Contributions of short-lived radioiodines to thyroid doses received by evacuees from the Chernobyl area estimated using early in vivo activity measurements. *Radiat Prot Dosimetry* 105(1-4): 593-599
- BEIR V (2005) Biological Effects of Ionizing Radiation V. Health risk from exposure to low level of ionizing radiation. Washington, DC.: National Academy of Sciences
- BEIR VII Phase 2 (2006) Biological Effects of Ionizing Radiation VII. Health risks from exposure to low level of ionizing radiation. Washington, DC.: National Academy of Sciences
- Bouville A, Linet MS, Hatch M, Mabuchi K, Simon SL (2014) Guidelines for exposure assessment in health risk studies following a nuclear reactor accident. *Environ Health Perspect* 122(1): 1-5
- Brenner AV, Tronko MD, Hatch M, et al. (2011) I-131 dose response for incident thyroid cancers in Ukraine related to the Chernobyl accident. *Environ Health Perspect* 119(7): 933-939
- Bromet EJ, Havenaar JM, Guey LT (2011) A 25 year retrospective review of the psychological consequences of the Chernobyl accident. *Clin Oncol (R Coll Radiol)* 23(4): 297-305
- Bromet EJ (2012) Mental health consequences of the Chernobyl disaster. *J Radiol Prot* 32(1): N71-N75
- Bromet EJ (2014) Emotional consequences of nuclear power plant disasters. *Health Phys* 106(2): 206-210
- Bromet EJ, Luft BJ (2015) Consequences of toxic disasters for rescue, recovery, and clean-up workers require integrated mental and physical health monitoring: Editorial comment for social psychiatry and psychiatric epidemiology. *Soc Psychiatry Psychiatr Epidemiol* 50(11): 1761-3
- Cardis E, Howe G, Ron E, et al. (2006) Cancer consequences of the Chernobyl accident: 20 years after. *J Radiol Prot* 26(2): 127-140
- Cardis E, Hatch M (2011) The Chernobyl accident - an epidemiological perspective. *Clin Oncol (R Coll Radiol)* 23(4): 251-260
- Chumak V, Krjuchkov V, Musijachenko NV, Bakhanova E (2000) Dosimetric monitoring at time of Chernobyl clean-up: a retrospective view.
- Chumak VV, Sholom SV, Bakhanova EV, Pasalskaya LF, Musijachenko AV (2005) High precision of EPR dosimetry as a reference tool for validation of other techniques. *Appl Radiat Isot* 62(2): 141-146
- Chumak VV (2007) Physical dosimetry of Chernobyl cleanup workers. *Health Phys* 93(5): 452-461
- Chumak VV, Worgul BV, Kundiyevev YI, et al. (2007) Dosimetry for a study of low-dose radiation cataracts among Chernobyl clean-up workers. *Radiat Res* 167(5): 606-614
- Drozdovitch V, Khrouch V, Maceika E, et al. (2010) Reconstruction of radiation doses in a case-control study of thyroid cancer following the Chernobyl accident. *Health Phys* 99(1): 1-16
- Drozdovitch V, Minenko V, Khrouch V, et al. (2013) Thyroid dose estimates for a cohort of Belarusian children exposed to radiation from the Chernobyl accident. *Radiat Res* 179(5): 597-609
- Drozdovitch V, Minenko V, Golovanov I, et al. (2015) Thyroid Dose Estimates for a Cohort of Belarusian Children Exposed to (131)I from the Chernobyl Accident: Assessment of Uncertainties. *Radiat Res* 184(2): 203-218

- Drozdovitch V, Chumak V, Kesminiene A, et al. (2016) Doses for post-Chernobyl epidemiological studies: are they reliable? *J Radiol Prot* 36(3): R36-R73.
- Fucic A, Aghajanyan A, Druzhinin V, et al. (2016) Follow-up studies on genome damage in children after Chernobyl nuclear power plant accident. *Arch Toxicol Epub* ahead of print.
- Hatch M, Ostroumova E, Brenner A, et al. (2015) Non-thyroid cancer in Northern Ukraine in the post-Chernobyl period: Short report. *Cancer Epidemiol* 39(3): 279-83.
- Hatch M, Brenner A, Bogdanova T, et al. (2009) A screening study of thyroid cancer and other thyroid diseases among individuals exposed *in utero* to iodine-131 from Chernobyl fallout. *J Clin Endocrinol Metab* 94(3): 899-906
- Havenaar JM, Cwikel J, Bromet EJ (2002) Toxic turmoil: psychological and societal consequences of ecological disasters. Springer Science & Business Media.
- Kashcheev VV, Chekin SY, Maksioutov MA, et al. (2015) Incidence and mortality of solid cancer among emergency workers of the Chernobyl accident: assessment of radiation risks for the follow-up period of 1992-2009. *Radiat Environ Biophys* 54(1): 13-23.
- Kashcheev VV, Chekin SY, Maksioutov MA, et al. (2016) Radiation-epidemiological study of cerebrovascular diseases in the cohort of Russian recovery operation workers of the Chernobyl accident. *Health Phys* 111(2): 192-7.
- Kesminiene A, Evrard AS, Ivanov VK, et al. (2008) Risk of hematological malignancies among Chernobyl liquidators. *Radiat Res* 170(6): 721-735
- Kesminiene A, Evrard AS, Ivanov VK, et al. (2012) Risk of thyroid cancer among Chernobyl liquidators. *Radiat Res* 178(5): 425-436
- Kryuchkov V, Chumak V, Maceika E, et al. (2009) Radrue method for reconstruction of external photon doses for Chernobyl liquidators in epidemiological studies. *Health Phys* 97(4): 275-298
- Laidra K, Rahu K, Tekkel M, Aluoja A, Leinsalu M (2015) Mental health and alcohol problems among Estonian cleanup workers 24 years after the Chernobyl accident. *Soc Psychiatry Psychiatr Epidemiol* 50(11): 1753-60
- Likhtarov I, Kovgan L, Chepurny M, et al. (2011) Estimation of the thyroid doses for ukrainian children exposed *in utero* after the chernobyl accident. *Health Phys* 100(6): 583-593
- Likhtarov I, Kovgan L, Masiuk S, et al. (2014) Thyroid cancer study among Ukrainian children exposed to radiation after the Chornbyl accident: improved estimates of the thyroid doses to the cohort members. *Health Phys* 106(3): 370-396
- Loganovsky K, Havenaar JM, Tintle NL, Guey LT, Kotov R, Bromet EJ (2008) The mental health of clean-up workers 18 years after the Chernobyl accident. *Psychological Medicine* 38(4): 481-488
- Ostroumova E, Gudzenko N, Brenner A, et al. (2014) Thyroid cancer incidence in Chornobyl liquidators in Ukraine: SIR analysis, 1986-2010. *Eur J Epidemiol* 29(5): 337-342
- Ostroumova E, Hatch M, Brenner A, et al. (2016) Non-thyroid cancer incidence in Belarusian residents exposed to Chernobyl fallout in childhood and adolescence: Standardized Incidence Ratio analysis, 1997-2011. *Environ Res* 147: 44-9.
- Prysyazhnyuk A, Gristchenko V, Fedorenko Z, et al. (2007) Twenty years after the Chernobyl accident: solid cancer incidence in various groups of the Ukrainian population. *Radiat Environ Biophys* 46(1): 43-51.

- Pukkala E, Kesminiene A, Poliakov S, et al. (2006) Breast cancer in Belarus and Ukraine after the Chernobyl accident. *Int J Cancer* 119(3): 651-8.
- Rahu K, Rahu M, Tekkel M, et al. (2015) Chernobyl cleanup workers from Estonia: cohort description and related epidemiological research. *J Radiol Prot* 35(4): R35-45.
- Rahu K, Bromet EJ, Hakulinen T, et al. (2014) Non-cancer morbidity among Estonian Chernobyl cleanup workers: a register-based cohort study. *BMJ Open* 4(5): e004516.
- Rahu K, Rahu M, Tekkel M, Bromet E (2006) Suicide risk among Chernobyl cleanup workers in Estonia still increased: an update cohort study. *Ann Epidemiol* 16(12): 917-919
- Rahu K, Auvinen A, Hakulinen T, et al. (2013, a) Chernobyl cleanup workers from Estonia: follow-up for cancer incidence and mortality. *J Radiol Prot* 33(2): 395-411
- Rahu K, Hakulinen T, Smailyte G, et al. (2013, b) Site-specific cancer risk in the Baltic cohort of Chernobyl cleanup workers, 1986-2007. *Eur J Cancer* 49(13): 2926-2933
- Rahu M, Rahu K, Auvinen A, et al. (2006) Cancer risk among Chernobyl cleanup workers in Estonia and Latvia, 1986-1998. *Int J Cancer* 119(1): 162-168
- Stepanenko VF, Voilleque PG, Gavrilin YI, et al. (2004) Estimating individual thyroid doses for a case-control study of childhood thyroid cancer in Bryansk Oblast, Russia. *Radiat Prot Dosimetry* 108(2): 143-160
- Stezhko VA, Buglova EE, Danilova LI, et al. (2004) A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: objectives, design and methods. *Radiat Res* 161(4): 481-492
- Tekkel M, Rahu M, Veidebaum T, et al. (1997) The Estonian study of Chernobyl cleanup workers: I. Design and questionnaire data. *Radiat Res* 147(5): 641-652
- Thomas G, Unger K, Krznaric M, et al. (2012) The chernobyl tissue bank - a repository for biomaterial and data used in integrative and systems biology modeling the human response to radiation. *Genes (Basel)* 3(2): 278-290
- UN Chernobyl Forum Expert Group "Health" (2006) Health Effects of the Chernobyl Accident and Special Health Care Programmes. In: Bennett B, Repacholi M, Carr Z, eds. Geneva: World Health Organisation
- UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2008) UNSCEAR 2006 Report - Effects of Ionizing Radiation. Volume I Report to the General Assembly / Scientific Annexes A and B. New York: United Nations
- UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2011) Sources and effects of ionizing radiation. In: UNSCEAR, ed. Report 2008-Volume 2. Annex D - Health effects due to radiation from the Chernobyl accident. New York: United Nations
- UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2010) Summary of low-dose radiation effects on health. New York: United Nations
- Weinberg HS, Korol AB, Kirzhner VM, et al. (2001) Very high mutation rate in offspring of Chernobyl accident liquidators. *Proc Biol Sci* 268(1471): 1001-5.
- Worgul BV, Kundiyevev YI, Sergiyenko NM, et al. (2007) Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat Res* 167(2): 233-243
- Yauseyenko V, Drozdovitch V, Ostroumova E, et al. (2016) Construction of cohort of persons exposed

- in utero* in Belarus following the Chernobyl accident. Medical and Biological Problems of Life Activity 1(15): 115-23 (in Russian)
- Zablotska LB, Ron E, Rozhko AV, et al. (2010) Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. Br J Cancer 104(1):181-7.
- Zablotska LB, Bazyka D, Lubin JH, et al. (2013) Radiation and the risk of chronic lymphocytic and other leukemias among chornobyl cleanup workers. Environ Health Perspect 121(1): 59-65
- Zvonova I.A., Balonov MI, Bratilova AA (1998) Thyroid dose reconstruction for the population of Russia after the Chernobyl accident. Rad Prot Dos 79: 175-178

## Annex: Time frame and milestones for deciding on further steps



## List of Milestones:

M1: Year 2 - Decisions on further analytical epidemiological and molecular biology studies in liquidators.

M2: Year 6 - Results of analytical epidemiological and molecular biology studies in liquidators.

M3: Year 3 - Decision on possible pooling of UkrAm and BelAm cohorts (ongoing NCI action).

M4: Year 3 - Decision on launching studies of neurobehavioral and cognitive effects following exposure *in utero*.

M5: Year 2 - Decision on further studies on offspring.

M6: Year 2 - Decision on feasibility of evacuees' cohort construction.

M7: Year 3 - Decision on multidisciplinary studies in residents of contaminated territories.