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COORDINATION OF STUDIES OF HEALTH RISKS IN THE CHERNOBYL CLEAN-UP WORKERS AND THEIR OFFSPRING IN THE BALTIC COUNTRIES

Report on a WHO Consultation

Helsinki
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EUR/HFA TARGET 18

This activity was organized by the WHO Regional Office for Europe to promote work aimed at achieving the following target in the health for all strategy.^a

TARGET 18

POLICY ON ENVIRONMENT AND HEALTH

By the year 2000, all Member States should have developed, and be implementing, policies on the environment and health that ensure ecologically sustainable development, effective prevention and control of environmental health risks and equitable access to healthy environments.

Keywords

ENVIRONMENTAL EXPOSURE
RISK FACTORS
OCCUPATIONAL HEALTH
NUCLEAR REACTORS
ACCIDENTS
RADIATION EFFECTS

ESTONIA
LATVIA
LITHUANIA
UKRAINE
CCEE

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^a *Updating of the European HFA targets.* Copenhagen, WHO Regional Office for Europe, 1991 (document EUR/RC41/Inf.Doc./1 Rev.1).

Consultation on the coordination of studies of health risks
in the Chernobyl clean-up workers and their offspring
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REPORT

Background

Following the Chernobyl accident, large numbers of mainly male workers were used to clean-up at the site of the accident and in districts more remote where contamination was found. As a consequence, very large populations (in excess of 400 000 persons) exist whose exposure to radiation is relatively high. Because many were drawn as conscripts from the military, these persons are widely dispersed within the states and countries of the former Soviet Union.

A formal request was made by the Ministries of Public Health of the Baltic countries to the World Health Organization, Regional Office for Europe for assistance in the tracing and following up of populations of clean-up workers living in the Baltic countries. Initial enquiries, however, established that activities with a similar aim were already either in progress or being planned. In consultation with these groups, it was decided that it would be beneficial for all persons involved to hold a meeting to review the progress of these activities, consider possible future developments, and, in particular, ensure that the various studies carried out in or planned for the Baltic countries were coordinated with one another and with other existing or planned activities in other parts of the former Soviet Union.

Such a meeting, organized by the WHO Regional Office for Europe (WHO/EURO) from the European Centre for Environment and Health (Rome Division), was set up in Helsinki, hosted by the Finnish Cancer Registry, and funded by the Swiss government. Participants included investigators from Estonia, Latvia and Lithuania, Sweden and Finland, as well as representatives from the International Agency for Research on Cancer (IARC) and the European Centre for Environment and Health (ECEH) (Rome Division) of the WHO for Europe. Because of the difficulties foreseen in obtaining reliable and precise dose estimates for the clean-up workers, an expert in the techniques of biological dosimetry was also invited to attend. The list of participants is attached as Appendix A.

The meeting lasted two days; the first day was devoted to presentations and the second to discussion of possible coordination and of future plans. The programme is attached as Appendix B. The presentations are summarized below.

Presentations

1. Estonian Chernobyl clean-up workers' cohort and planned studies (by M. Rahu)

In 1991, Estonian investigators contacted their counterparts in several countries seeking assistance for the setting up of a registry of persons exposed as a result of the Chernobyl accident in Estonia, and for its use in a study of leukemia among Chernobyl clean-up workers. The same year, an agreement was drawn up with the Finnish Cancer Registry, the Finnish Centre for Radiation and Nuclear Safety, and the Radiation Epidemiology Branch of the US National Cancer Institute for the conduct and funding of such a study. A protocol was prepared. The final version will be available shortly.

The study started on 1 April 1992. It is designed as a cohort study of all males who participated in the clean-up and reconstruction activities in the Chernobyl area following the accident during the period 1986-1990. It will cover between 4 200 and 5 000 persons. The study will last until 1 April 1995, with a follow-up for leukemia incidence up to 1 April 1994. Comparisons will be made between the incidence of leukemia in the clean-up workers and that of the male population of Estonia; internal comparisons by level of dose within the cohort will also be carried out. Efforts are currently being concentrated on three main areas: identification of the cohort, validation of biological dosimetric techniques, and drafting of an extensive mail questionnaire which will cover various aspects of the work experience at Chernobyl, previous occupational and exposure histories, and information on children born before and after the accident.

Cohort identification is based on four sources of information: the military lists of the Estonian Defense Force; the Estonian Chernobyl Radiation Registry; the records of the Estonian Chernobyl Committee, and those of the Estonian Ministry of Social Welfare Registry.

The Estonian Defense Force has access to records of the ex-Soviet Army on persons who were either specifically drafted for the clean-up of the accident or who were sent to perform this work as part of their regular military activity. These records were abstracted in 1990 for the Estonian Ministry of Health.

The Estonian Chernobyl Radiation Registry was organized in 1991 in response to public pressure to monitor health; it was set up as a follow-up centre responsible for medical check-ups of clean-up workers. It is located in the Fourth Hospital in Tallinn. All documents on the medical examinations conducted in Estonian hospitals on clean-up workers are maintained there (until recently two sets of documents were collected: one was kept in Tallinn, and the other was sent to the All-Union Register in Obninsk). In addition to military clean-up workers, information is available on a small number of civilians who were hired for the clean-up work at Chernobyl. The registry currently contains computerized information on 2 710 clean-up workers: 67% employed in 1986, 22% in 1987, 10% in 1988, 1% in 1989, and a small percentage in 1990.

The Estonian Chernobyl Committee was set up in 1988 as a pressure group to the Estonian Government. It is constituted of local committees which maintain lists of veterans interested in claiming benefits and compensations. The Estonian Ministry of Social Welfare has also constituted a register in order to provide some benefits for the veterans and their families. (At present, these benefits are: an additional month of pay every year and free access to sanatoria). The clean-up workers in this register were identified through newspaper advertisements, requesting that clean-up workers contact the local agencies of the Ministry in order to be registered; the deadline for registration was May 1, 1992. Proof of work in Chernobyl, in the form of a certificate or a stamp on the military passport, is required for inclusion in the registry.

Based on information currently available in the Chernobyl Radiation Registry, most of the workers were aged between 25 and 39 years at the time they worked in Chernobyl. Most of them wore thermoluminescent dosimeters (TLD); these were worn under protective clothing when such clothing was available. The TLDs were read by the military radiation staff at Chernobyl and doses registered in the military passports. Among the 2 710 workers currently in the registry, doses are unknown for 40%; it is hoped that doses can be obtained for an additional 15%. There is, however, concern about the validity of the registered doses in the military passports: a very large number of doses are estimated to be just below 250 mSv (which was the cutpoint used for limiting exposure to the clean-up workers); in addition, a larger number of workers than would be expected by chance have doses registered at 100 or 200 mSv.

A large majority of workers were employed between May and July of 1986; most of them worked for 4 to 6 months; 4% worked less than 1 month, 12.4% less than 2 months, and 14.4% less than 3 months. According to the newspaper reports published in Estonia, it would appear that Estonian clean-up workers stayed on average longer in the Chernobyl area than their Lithuanian and Latvian counterparts (1 to 2 months).

The follow-up will be based on record linkage with three different sources: the Estonian Cancer Registry, the death certificate registry, and the population registry. The Estonian Cancer Registry was set up in 1978 but data have been centrally kept since 1968. All the information needed for linkage to the Chernobyl Registry (such as name and date of birth) is available. The Cancer Registry has been a member of the International Association of Cancer Registries since 1989, and data from it will be included in the next volume of the IARC publication "Cancer Incidence in Five Continents".

The death certificate registry has been computerized since 1986. Historically, however, neither name nor identity number was available in its records. Names were introduced this year, and national identity numbers are being introduced and the records redesigned. At this time, therefore, follow-up based on the death certificate registry will imply manual processing and cannot be done via computerized linkage.

The population registry is maintained at the local and centralized levels. All persons over the age of 15 are included. It is not at present computerized and its use for identifying persons who have moved or who have died implies manual processing. It is hoped that this registry will be computerized in the future. Information is available in this registry on nationality: approximately 35% of registered persons are non-Estonian nationals.

The power of the study of leukemia risk among Estonian clean-up workers is clearly very low, given the small expected number of cases in a population of approximately 5 000 workers. However, this study is feasible, and may stimulate other countries, in particular other Baltic countries, to participate using similar protocols, thus substantially increasing the power of the study.

It is clearly important for internal comparisons within the cohorts of clean-up workers to obtain precise estimates of exposure or dose. At present, only the physical dose estimates in the military passports are available. There is some concern that these may not be accurate. Blood samples will soon be collected during regular medical examinations on a sub-group of clean-up workers, with the aim of carrying out a biological assessment of dose in the future using chromosome painting or the glycophorin-A assay. The protocol agreed with the US National Cancer Institute (US NCI) includes inter-comparison studies of currently available biological dosimetric techniques.

2. Latvian Chernobyl clean-up workers' cohort and planned studies (by A. Stengrevics)

In Latvia, the general situation for follow-up of clean-up workers is similar to that of Estonia. According to the reports of the Soviet military, there were 6 475 Latvian workers involved in the clean-up of the Chernobyl accident. In addition to the clean-up workers themselves, Latvian investigators are concerned about the health consequences of the accident on children of the clean-up workers, on evacuated persons from the Chernobyl area (many have been relocated to Latvia) and to a lesser extent on the general population of the country.

The main source of information to identify Latvian clean-up workers is the Chernobyl Registry based in the Chernobyl Centre, which currently holds data on approximately 4 500 clean-up workers. The Chernobyl Centre is based in the outpatient department of the Republic's Clinical Hospital in Riga. It is the Health Department Unit in charge of follow-up of clean-up workers. A number of medical specialists work there and are involved in registration of disease, diagnosis, treatment, and hospitalization. Staff at the Centre currently report that approximately 60% of the clean-up workers are ill; of these, 12% are reported to be disabled, with diseases of the skeleton and muscles, respiratory, nervous, digestive or immunological systems.

Military records have been missing since August 1991 and can therefore not currently be used for identifying clean-up workers.

Based on information currently contained in the Chernobyl registry, it appears that many of the clean-up workers from Latvia reside in Riga. These workers were mainly between the ages of 20 and 39 at the time of work. Those employed between 1986 and 1987 worked for an average of 1 to 3 months, while those employed later worked for 4 to 6 months on average. The workers employed in 1988-1989 were mainly occupied with building a town near the Chernobyl reactors and did not intervene on the site of the reactor itself; their doses are therefore lower on average than those of earlier clean-up workers.

As in Estonia, the follow-up of the clean-up workers can be based on the cancer registry, the population registry and the death certificate registry. The possibility of joining the US National Cancer Institute (NCI) epidemiological study is being considered, as is that of obtaining blood samples on approximately 1 000 clean-up workers and freezing the lymphocytes for future biological dosimetric analyses at the Finnish Centre for Radiation and Nuclear Safety.

No funding is currently available for a study of clean-up workers in Latvia. Applications will be made to the US NCI; information on other potential sources of funding would be appreciated.

There is a need for training of epidemiologists from Latvia. Possible host institutions and sources of financing will be identified and communicated to the local investigators.

It was suggested that investigators at the Cancer Registry could consider joining the IARC ECLIS study.

3. Lithuanian Chernobyl clean-up workers' cohort and planned studies (by R. Gurevicius)

The situation for setting up an epidemiological study of leukemia risk in Lithuanian clean-up workers is very similar to that of Estonia. Lithuania is the largest of the Baltic countries (3.7 million persons living in 44 regions) with approximately 10 000 cancer cases (crude incidence rate of 273 per 10⁵) and 7 000 cancer deaths per year (crude mortality rate of 190 per 10⁵).

The questionnaire and methods developed for the Estonian study have been reviewed and endorsed by the Lithuanians with slight modifications (one question was added on the questionnaire about alcohol consumption). The primary source for identification of the cohort is the Chernobyl Medical Centre which was created in 1991 with the aim of following up the persons exposed as a result of the accident. It is estimated that over 7 000 clean-up workers from Lithuania were involved in the Chernobyl area. At present, 3 813 clean-up workers have responded to the questionnaire, and approximately 2 000 have received a medical examination at the Chernobyl Centre.

An additional source of data for identification of the cohort is a list compiled by the Lithuanian Parliament of clean-up workers identified through newspaper advertisements requesting Chernobyl veterans to be registered for compensation purposes. As in Estonia, proof of participation in the Chernobyl clean-up was required.

Based on information currently held at the Chernobyl Centre, 50% of the workers were between 31 and 40 years old at the time of the clean-up activities, while 20% were between the ages of 21 and 30.

As in Estonia, estimates of doses are available in military records. These doses are missing for approximately 29% of the registered workers. Follow-up of the cohort will be based, as in Estonia, on the Cancer Registry, the population registry and the death registry. Some studies of chromosomal aberrations - mainly counts of dicentric - are currently under way. A random sample of 20 clean-up workers was chosen and their chromosomes analysed. The rate of dicentric in these persons was ten times higher than that of population controls.

Although an epidemiological study of clean-up workers has already started in Lithuania, with a protocol similar to that being developed in Estonia, there is no external financial support for this study yet. The US National Cancer Institute will be approached for funding, as well as other organizations if information can be obtained about these. The estimated cost of the study for three years is US\$ 200 000.

4. IARC feasibility studies on Chernobyl clean-up workers (by E. Cardis)

IARC is currently planning to carry out an extensive feasibility study in the three most affected states of Belarus, Russia, and Ukraine to investigate whether long-term follow-up studies of persons exposed as a result of the Chernobyl accident, aimed at answering a number of scientific questions, are feasible. These include questions about the effects of mainly external exposures in clean-up workers and in their offspring. The outline and background to the feasibility study are available as Appendix C.

5. Second generation studies of Chernobyl clean-up workers' offspring (by L. Ehrenberg)

Studies of persons exposed as a result of the Chernobyl accident, in particular the clean-up workers and their offspring, may be useful in providing additional information about the shape of the dose response for cancer risk at low doses of ionizing radiation. In experimental studies, non-linear dose responses have been seen in the low dose range; however, several of these experiments have shown that the dose response became linear when the radiation exposure was given in combination or followed by the promoter TPA. In humans, at this time, there appears to be little evidence of a non-linear dose response in the low dose range. For clarity, low doses are defined here as doses below 3 mGray (the level of dose resulting on average, in 1 hit per cell nucleus).

In 1991, an agreement was made between the Royal Swedish Academy of Sciences and the Academy of Sciences of the former USSR, to study cancer risk in the second generation, specifically in the offspring of exposed workers.

As a result, a visit to the Russian Federation was carried out in the spring of 1992. No particular design or protocol has yet been developed, although possible designs include cohort and case-control designs for the study of cancer risk in the children of the clean-up workers.

There are some questions about the power which such a study might have: there is anecdotal evidence that the number of conceived children was limited among the clean-up workers during the first years following the accident, since many physicians recommended delaying conception. In Estonia, moreover, only married men who already had 2 or more children were sent to the Chernobyl area for clean-up work, at least from 1987. If this practice was prevalent in the rest of the former USSR, it would severely limit the size of the cohort of clean-up workers having conceived in the first years following the Chernobyl accident. It is likely, however, that for the early clean-up workers at least (i.e., those who received fairly high doses in a very short period of time and in which presumably the relative risks would be the highest), no such selection was carried out. That group of workers, however, is one for which the dosimetry is likely to be the poorest; it is therefore important to target this group in the determination of the usefulness of biological techniques for assessing levels of exposure. Blood samples from these workers could be collected and stored for later examination of chromosome aberrations, as well as possible gene mutations in the lymphocytes of clean-up workers whose children have developed cancer.

6. WHO European Centre for Environment and Health - Plans for Chernobyl clean-up workers studies and their support in the Baltic countries and elsewhere (by K. Baverstock)

The WHO/EURO European Centre for Environment and Health, with operating divisions in Rome, Italy, and Bilthoven, Netherlands, and a project office in Nancy, France, has been set up to address the global concern of environment and health. Its mandate is to provide guidelines for "improvement of health and of well-being", and to "strengthen collaboration among European countries on the health aspects of environmental protection, with special emphasis on information systems, mechanisms for exchanging experiences and coordinating studies". The radiation programme, located at the Rome Division, must therefore specifically address radiation issues of concern to the European populations. In general, the European populations tend to be more concerned about nuclear accidents than about ambient radiation exposures, apart from those resulting from environmental radon levels in some countries.

The Rome division provides advice and technical assistance in the early diagnosis of conditions associated with radiation, and attempts to identify circumstances requiring epidemiological investigations (such as the reported epidemic of thyroid cancers in the children of Belarus). In addition, given the important psycho-social effects noted following the Chernobyl accident, the Rome centre is developing a programme of technical assistance aimed at educating key persons in the society to provide appropriate advice and information to persons concerned about the effects of ionizing radiation.

There are a number of unresolved issues in radiation protection today, in particular the magnitude of effects of radiation at low doses and specifically at low dose rates. Epidemiologic studies of the consequences of the Chernobyl accident could help to resolve some of these difficulties. At this time, a large number of efforts are being planned or carried out by investigators from the various states of the former USSR, individually or in collaboration with researchers from Europe, America and Asia. Reports indicate that different studies are being planned or implemented on overlapping populations in an uncoordinated fashion. Such a situation may lead to studies of similar issues reporting conflicting results; this would not reassure the populations about the level of expertise available on the effects of low doses of ionizing radiation.

This situation has arisen in part due to the lack of specific epidemiological expertise in Belarus, Ukraine, and to a lesser degree in the Russian Federation. It is therefore proposed that the WHO/EURO European Centre for Environment and Health in Rome be the centre for international collaboration with the NIS with respect to epidemiological studies of the Chernobyl consequences. It proposes to provide expertise to the states of the former USSR, and to ensure the coordination of planned or on-going studies, initially by providing information about existing efforts and about possible sources of funding.

7. Possibilities of dose reconstruction on the basis of biological dosimetry (by A.T. Natajara)

The frequency of chromosomal aberrations can serve as a possible "biological dosimeter" in the case of radiation accidents, such as that of Goiania in Brazil. There are two main types of chromosomal aberrations: structural aberrations (stable and unstable) which are dose-dependent, and numerical aberrations (hypoploidy, polyploidy, ...) which are induced by ionizing radiation but do not appear to be dose-dependent.

Unstable aberrations come from misrepair of DNA double or single strand breaks (which are repaired within ten minutes of occurrence); they include dicentrics and micronuclei. Dicentrics carrying lymphocytes can persist for years in the human body. However, dicentrics are unstable aberrations and when a lymphocyte carrying a dicentric, the daughter cells will most probably die due to chromosomal segregation problems. The frequency of these aberrations is dose-related and, for low LET radiation, is also dose-rate dependent. For high LET radiation, the dose response appears to be linear. Standard calibration curves for high and low LET radiation and for different dose rates have been established. It is therefore possible not only to infer dose from cytogenetic analysis of samples of blood, but to distinguish between: whole body and partial body exposures (over-dispersion of the Poisson distribution); acute vs. chronic exposures; high vs. low LET; and mixtures of radiation types.

This approach has been applied immediately following the accident in Goiania, Brazil (where 1 300 Ci of cesium 137 was dispersed). Both internal dosimetry, including bioassay and whole body monitoring, and cytogenetics (estimations of dicentrics for external radiation exposure) were performed on exposed subjects. Follow-up analyses are being carried out in order to study and characterize trends in frequency of dicentrics over time. The half life of lymphocytes, previously estimated by the NRPB to be approximately 3 years, appears, in the Goiania follow-up, to range between 180 and 300 days. Although dicentrics may persist for years, these are called unstable as, when the lymphocytes divide, they will either die or give rise to reciprocal translocations.

Reciprocal translocations are balanced, stable aberrations, and these will remain for many decades. Molecular biological studies indicate that reciprocal translocations are associated with activation of oncogenes which are situated at specific break points of the chromosomes involved, in most human tumour types. The frequency of reciprocal translocations can be estimated by G-banding; this technique, however, is very time consuming and requires very good preparations of the lymphocytes.

An alternative technique, called "chromosome painting" or FISH (fluorescent in-situ hybridization), relies on *in-situ* hybridizing appropriately labelled DNA libraries of specific human chromosomes to metaphase chromosome preparations. A hybridization signal is detected by using specific antibodies hooked to a fluorochrome, viewed under a fluorescent microscope. When chromosomes are stained, the translocations can be scored in a straightforward manner. It is now possible to stain or "paint" up to 11 pairs of chromosomes, but the resolution for scoring of translocations is poor; much better resolution for reciprocal, terminal and interstitial translocations is obtained when only 3 chromosomes at a time are painted. There also exists a technique to paint only the centromeres, and thus score the dicentrics. In cells irradiated *in vitro* and examined immediately, a good estimate of doses can be obtained when using two different sets of three painted chromosomes. At low levels, more translocations are picked up than dicentrics. The technique of chromosome painting has been applied by researchers at Lawrence Livermore Laboratory in the USA to lymphocytes from several atomic bomb survivors and some workers involved in the criticality flash at the Oakridge National Laboratory Y-12 plant; in the latter case, the frequency of translocations scored by chromosome painting was not related to the estimated dose level, possibly because of the non-homogeneity of the dose received. This technique appears promising, however, for whole-body exposures received in a short amount of time; validation studies do need to be carried out, however, and the variation in the frequency of scorable translocations with time should be evaluated if this technique is to be used for retrospective dose estimation, especially in the case of Chernobyl where exposures were received over six years ago.

Cardis:

It is clear that there is much public concern about the consequences of the Chernobyl accident. If no scientifically sound study addressing any of the issues of quantitative risk assessment and radiation protection appears to be feasible, it may be reasonable to focus instead on general studies of the global public health impact of the accident. Such studies imply different and simpler designs, do not rely so heavily on the precision of dose estimates and are much cheaper to conduct. In addition, a study aimed at quantitative risk assessment may not respond to the public concern since it would necessarily be a very careful study of a much more limited population.

Ehrenberg:

Studies of the effects on the second generation are worthwhile since we have little knowledge about such effects at this time, even if we do not know the possible cohort size and the shape of the dose responses in this dose range. It is important to start such studies now in the countries where they are feasible, and to encourage such studies to be started elsewhere when they become feasible.

Hakama:

Soon after the accident, the prediction of effect was several hundred to several thousand extra cancer deaths attributable to the accident worldwide. However, the consequences are conceived by the public to be much greater. It is therefore our responsibility to allay public concern, and to focus on studies aimed at evaluating the global public health impact if scientific studies cannot be carried out.

Cardis:

Studies of leukemia risk in clean-up workers in the Baltic countries are worthwhile because they are relatively inexpensive and easy to carry out.

Ehrenberg:

Such studies in the Baltic countries can be thought of as pilot studies; they will help to gain experience for setting up studies of larger numbers of clean-up workers in the most affected states of the ex-USSR.

Conclusion:

It is worthwhile to set up such studies in the Baltic countries.

SECOND ISSUE: Is it possible to carry out epidemiological studies of the Chernobyl consequences?

(a) Dosimetry

Precise determination of doses of clean-up workers is currently problematic. New techniques seem promising, and in all probability in a few years they will have been validated and shown to be useful at least on part of the dose range of concern to us for such studies. It is clear that the existing military records are probably unreliable.

Hakulinen:

It is unlikely that the real records have been kept by the ex-Soviet military. It is also possible that only the high doses are falsified.

Rytömaa:

Even if other lists exist and are found, it is not clear whether they would be better. In particular, the estimates of doses recorded from the dosimeters would be useless for persons who have inhaled or ingested particles of uranium. If doses cannot be estimated correctly, they will not be of help for dose-response analysis.

Natarajan:

The new biological dosimetry techniques will probably be validated in several years, and it is expected that they will be sensitive down to levels of .25 Gy.

Cardis:

.25 Gy is not very optimistic for epidemiological studies since this is, theoretically, the upper range of doses for clean-up workers; this would not allow any dose response analysis to be carried out.

Ehrenberg:

In the future, these methods will be better and the biological dosimetry will be useful. Studies of DNA damage will also be useful.

Bertolini:

Perhaps the answers to the questionnaire could provide a better approach for classifying workers in broad dose categories.

Cardis:

If there is no prospect for accurate dosimetry in the range <20 to 250 mGy, we will not learn any more about dose response in the low dose range; it may be better to plan now on studies with a different aim, such as estimating the global public health impact.

Rytömaa:

There will be developments in the future, of course. However, there are no prospects for really sensitive and specific methods in the near future.

Baverstock:

It may be interesting to look at the effect of dose rate by separating, from the questionnaire, workers who have worked on the roof of the reactor and thus received very high dose rates, and those who have worked elsewhere and thus received low dose rates. Even if there is no knowledge of the total dose, one could test whether low dose rates are as efficient in inducing cancer as high dose rates.

Cardis:

Given the small magnitude of the doses, it is probable that we won't be able to characterize any increases and therefore we will not be able to differentiate between the effects of high and low dose rates.

Ehrenberg:

Studies of the offspring of the Chernobyl workers can serve to test the hypothesis of an increased risk of leukemia in children following exposure of the father in a small window of time before conception (Gardner et al., 1990).

Cardis and Rytömaa:

It is unlikely that this hypothesis could be tested in the current circumstances (unknown doses, small numbers, ...).

Baverstock:

For the purpose of validation of biological dosimetry, it may be possible to find a sample of the population willing to give one whole tooth, some blood, and to answer a questionnaire. The glycophorin-A assay and chromosome painting can then be applied to the blood sample and electron spin resonance to the tooth. Electron spin resonance of teeth enamel would be the true estimate of dose and would serve to validate the other two techniques. Such a study could usefully be made quite quickly.

Rahu:

Much of the falsification of official doses is probably among those workers recorded as having 100 or 200 mGy. The prospect of getting whole teeth from volunteers is uncertain.

Natarajan:

A meeting will be held in July with the Commission of the European Communities to discuss biological dosimetry. This should lead to coordination and comparison of work in three laboratories: Leiden, Munich (GSF), and the NRPB.

(b) CoordinationHakulinen:

A Baltic forum could be set up for the coordination of the Baltic countries. The Finnish Cancer Registry could play a role in advising this forum, and WHO could play a facilitating role, especially on issues of funding and training.

Gurevicius:

A Baltic forum is a good idea. There is great need for training, and fellowships such as ICRETT should be identified.

Veidebaum:

Most of the information sent from WHO is usually sent to ministries rather than to the concerned investigators. There is a need for money to print translated books, and also for information on training. These should go directly to the investigators rather than to the ministries.

Bertolini:

A committee should be set up, consisting of one or two investigators per country. If this committee agrees on a joint protocol for the clean-up workers study, WHO will help in getting the funding. WHO can also organize a course in basic epidemiology in the Baltic countries or selected investigators can attend existing IARC courses. One or two persons should be selected per country for training over longer time periods.

Hakama:

The University at Tampere gives a one-year training course in epidemiology of cancer, in English. This is a post-graduate course which teaches registration, study design and analysis. This may be an appropriate course for training of scientists from the Baltic countries.

Veidebaum:

The coordination should be with persons involved in the actual work; a committee of experts can be set up. The coordination should not be with the ministries.

Hakulinen:

A recommendation should be made to keep each other informed of work and of planned studies. Coordination is essential so that protocols are similar.

Bertolini:

The recommendation should be for Baltic countries to set up a committee for the first purpose of developing a protocol for a study of clean-up workers; the second purpose would be to better plan training needs. Once this committee has been organized, it can approach WHO with a proposal.

Hakulinen:

The recommendation should be for a coordinated and compatible protocol rather than a common protocol.

Ehrenberg:

The committee should not dictate all protocols. There must be room for new ideas and new studies. Sweden is also interested in working with the Baltic countries.

CONCLUSIONS AND RECOMMENDATIONS

1. The consequences of the Chernobyl accident are too important not to undertake any studies, even if there is no prospect of accurate dosimetry. Studies of clean-up workers and of their offspring therefore should go ahead.
2. The choice of priorities in the objectives of the study are clear. One should answer public health concern first, and then address scientific questions.
3. WHO/EURO is willing to play a facilitating role for the fundraising and coordination of these studies and the provision of training.
4. A committee of Baltic representatives should be set up to
 - (i) identify training needs,
 - (ii) initiate discussions and draw up the outlines of compatible protocols,
and
 - (iii) facilitate information exchange on other proposals.

This should be done by the end of August 1992. During that time, WHO will review opportunities for training and funding. The Baltic experts should decide among themselves who will be the representatives on the committee. The Baltic committee should also discuss how WHO/EURO can best be of assistance within its remit to provide epidemiological and radiological technical help.

5. The outcome of an epidemiological study should not be limited to cancer in directly exposed subjects; they should also include effects on the second generation, including congenital anomalies as well as general effects on reproductive health and on mental retardation. Birth defects are currently not registered, however, in the Baltic countries. Some thought is therefore needed for the planning of epidemiological studies of birth defects: lack of systematic registration would imply the need for more active surveillance.

As a first phase, the epidemiological studies should be directed at testing whether or not there is an increase in risk with respect to the baseline incidence in the general population. In the second phase, studies of dose response and of effects on other outcomes will be set up.

Contacts are taking place between ECEH, Rome and the International Centre for Birth Defects (ICBD) to set up a training programme on birth defects monitoring for the three Baltic countries.

6. Coordination is essential in order to avoid the possibility of a multiplicity of overlapping studies resulting in contradictory and misleading conclusions.

Feasibility study

Outline of the protocol for the feasibility study regarding possible Epidemiologic studies of the consequences of the Chernobyl accident to be carried out within the Council of Europe SIEAD/OPA/Chernobyl programme

BACKGROUND

The Chernobyl accident, which took place on 26 April 1986, resulted in widespread radioactive contamination over large areas of Belarus, Russia, Ukraine and, to a lesser extent, the Baltic States and the rest of Europe. Hundreds of thousands of persons, employed in the clean up of the accident or residing in the more contaminated areas of Belarus, Russia, and Ukraine, received substantial doses of radiation as a result.

Epidemiologic follow-up of these populations could yield answers to one or more of the following radiation protection and public health questions:

- what are the effects of low doses?
- what are the effects of dose protraction in the low dose range?
- what are the effects of internal contamination with I-131 and its interaction with possible confounding and effect-modifying factors on the risk of thyroid disease, especially in children?
- what are the transgenerational effects of exposure to ionizing radiation?
- what are the effects of internal contamination by actinides?

On 18 and 19 December 1991, the Epidemiology Study Group of the Medical Committee of the Council of Europe's SIEAD/OPA/Chernobyl programme met in Lyon to:

- review the current state of epidemiological initiatives planned or on-going for the follow-up of persons exposed as a result of the Chernobyl accident;
- identify specific scientific goals that could be achieved under the SIEAD/APO/Chernobyl programme of the Council of Europe; and
- discuss the need for an epidemiological feasibility study.

The list of participants to the meeting is given in Appendix A.

The participants concluded that a formal study of the feasibility of setting up long-term epidemiological studies to answer the questions listed above should be carried out. They recommended that this study be directed by Dr E. Cardis of IARC, and that a collaborative agreement be drawn up between IARC and the Council of Europe to cover it.

AIM OF THE FEASIBILITY STUDY

The aims of the feasibility study are:

1. To investigate whether, under the current activities of registration of exposed populations underway at the state level in Belarus, Russia, and Ukraine, as well as at the NIS level in Obninsk, and under the mandate of the Council of Europe which aims at strengthening this activity, it will be feasible to obtain data that would contribute usefully to answering some of the research questions listed above.

2. To review existing protocols covering the investigation and follow-up of currently registered populations and advise regarding the need, if any, for modifications that might increase their potential to answer these research questions.
3. To identify populations not at present subjects of a study or a proposed study, which, if followed up, would contribute to answering these questions and advise regarding the feasibility of undertaking such follow-up studies. Particular attention should be given to populations in the areas chosen for the pilot phase of the programme of the Council of Europe.
4. To prepare outline protocols for any new studies that might be considered feasible and justified as a result of this investigation.
5. To advise on the nature of the contribution that the Council of Europe might make to the conduct of any studies considered to be feasible having regard to the public health importance and likely scientific cost-effectiveness of the work and the nature and sources of other international contributions that are being made to it.

EXPECTED RESULTS OF THE FEASIBILITY STUDY

The primary result of the feasibility study will be a detailed report summarizing the research undertaken in the CIS by the Feasibility Study Group and its conclusions. If existing work is judged to be feasible, recommendations will be made, where appropriate, regarding ways in which its scientific and public health value can be enhanced. If one or more new studies is judged feasible and desirable, outline protocols will be prepared covering the specific scientific objectives of each study, definition of the study population, mechanisms for follow-up and for individual dose estimation, and the necessary conditions for the study to be fruitful in the long-term. If studies to answer any or all of the specific goals listed above are not judged to be feasible or desirable, the report will present a detailed justification for this conclusion.

ORGANIZATION OF THE FEASIBILITY STUDY

The feasibility study will be coordinated from Lyon by Dr E. Cardis in consultation with Dr K. Baverstock (Co-chairperson of the Epidemiology Study Group, WHO EURO Centre for Environment and Health, Rome), Dr J.P. Massué (Executive Secretary of the Open Partial Agreement on Major Risks at the Council of Europe), and members of the Medical Committee of the SIEAD/OPA/Chernobyl programme of the Council of Europe.

A study group consisting of Dr Cardis, several (2 to 4) consultants (epidemiologists from outside the affected states), and one adviser each from Belarus, Russia, and Ukraine will be set up to carry out the study. The consultants will be experienced occupational or environmental cancer epidemiologists. The advisers in each of the affected states will be epidemiologists or other experts actively involved in the planning and carrying out of epidemiological follow-up of the consequences of Chernobyl in their own state. They will participate, with the rest of the study group, in evaluation of the feasibility of studies designed to answer the specific questions listed above; in addition, they will serve as the primary scientific contact in their home state and facilitate collaboration with other persons involved locally in epidemiological research related to the Chernobyl accident.

Authorization for carrying out the feasibility study will be obtained by Dr Massué from the competent authorities in the affected states of Belarus, Russia, and Ukraine. Dr Cardis will be responsible for making the appropriate scientific contacts in the states in order to facilitate the conduct of the feasibility study. Advice and assistance will be sought in this process from the International Programme on Health Effects of the Chernobyl Accident (IPHECA) of the World Health Organization.

APPROACH

In any epidemiological study of cancer risk associated with radiation exposure, information is needed for each individual in the study on vital statistics (date of birth, date and cause of death, and/or date of diagnosis of cancer), and radiation exposure history. Additionally, other information on health history and environmental or occupational exposures may be of interest. This information often is collected from various independent sources; personal identifiers are therefore essential in order to ensure the proper linking of information from these various sources.

Factors which will affect the feasibility of a study of cancer risk among persons exposed occupationally or environmentally in Belarus, Russia, and Ukraine are described below. They are principally of three types: technical, logistic, and legal. They include the degree to which information is accessible centrally and computerized, the ease with which it can be linked to information on dosimetry, cancer mortality or morbidity, and other important factors. The cost of such a study will depend on the amount of information currently available centrally and computerized, and on the existing facilities for ensuring the linkage.

The information necessary to evaluate the feasibility of long-term epidemiological studies to answer one of the specific questions mentioned above will be obtained primarily through site visits to the concerned states. The main steps which must be taken to evaluate the feasibility are listed below:

Identification of study populations:

The first step involves a review of possible sources of information for identification of members of the study population. These sources include:

- the existing "Chernobyl registers" which are maintained in each of the affected states;
- military registers of persons employed as emergency accident workers; and
- state and local civil registers of persons living in given areas.

If long-term epidemiological studies to answer one of the above questions are carried out, the choice of the primary source of data for identification of the study population will be made after examination of sample records from each source and from different time periods, and after review of the selection criteria used for the inclusion of persons in each of these different registers.

Whichever source is chosen, it must be readily accessible, complete, and allow linkage with individual data on exposure and on cancer risk.

Sources and adequacy of dosimetric data:

In a second step, data on personal exposure to ionizing radiation, both external and internal, by year, will need to be obtained:

- Direct physical dosimetric estimates of dose from external exposure and from internal contamination are available respectively for tens of thousands and for hundreds of thousands of persons in the three affected states.

- Estimates based on modelling of exposure are available for large segments of the remaining populations.
- Dosimetric reconstruction, based on biological dosimetry (either spin electron resonance of teeth enamel or analysis of chromosomal aberrations) is currently under way or planned in several institutions in the affected states.

A number of international teams of experts have already carried out an in-depth review of the dosimetric information available in the three states (See for example IAEA, 1991). Their report will serve as a basis for evaluating the adequacy of the dosimetric information, both physical and biological, for the purposes of epidemiological studies of cancer risk as a result of radiation exposure. It is thought that the adequacy of the dose estimates will vary very much with dose level.

The advantages and disadvantages of using these different sources of dosimetric data will be reviewed. The difficulties and cost of carrying out biological dosimetry will be assessed. The source of dosimetric data may be different from study to study; it must be readily accessible, complete, and unbiased (if dose-dependent biases exist, they should be characterized and quantified), and the sources of data should be linkable with the other sources of data needed for an epidemiological study. Information on the practices for monitoring in different populations will also be obtained.

Mechanisms of follow-up:

The feasibility of various types of follow up (morbidity, mortality) will then be explored and estimates of costs and resources obtained. In states where morbidity registers do not exist, alternate sources will be sought for mortality follow-up; such sources include civil registers of persons living in a given republic or district and statewide health services systems. The possibility of setting up statewide cancer registries where these do not exist will be examined. It should be noted that when no central system is available for identifying deaths and causes of deaths or cancer cases, epidemiological studies tend to be much more costly and time- and personnel-consuming, and more open to possible bias than when such systems exist.

Other data:

The quality and availability of information on other factors of interest will also be assessed. Possible types of information include occupational history, smoking and alcohol consumptions and medical history. Sources for this information will be reviewed.

Training needs:

The state of the existing research resources and the possibility of developing/strengthening them sufficiently within an appropriate time frame and for sufficiently long to carry out these studies will also be evaluated.

Cost and feasibility:

Finally, the cost and the feasibility of linking all the sources of information identified in the above steps must be assessed. In some states, mechanisms may need to be set up in order to carry out linkage of the various sources of data; a small scale pilot study to ensure that the linkage is possible may then be desirable.

CONDUCT OF STUDY

The information necessary to evaluate the feasibility of long-term epidemiological studies of the consequences of the Chernobyl accident discussed above will be gathered through site visits of the Study Group to all three affected states. The primary contact in each state (the temporary adviser, member of the Study Group from each state) will be responsible for setting up appropriate meetings, and for participating during the site visits, as well as afterwards (during the feasibility evaluation period) in the collection and processing of information listed above.

The investigation process will last approximately one month for each of the affected states. Two of the consultants will participate at any time. The first week will be spent in Lyon preparing the visit. The second and third weeks will be spent in the particular state reviewing the possible study populations, the sources of information on radiation and other exposures, the characteristics of existing registers, and assessing whether adequate mechanisms exist or can be set up to ensure long-term epidemiological follow up. These site visits will mainly be carried out to institutes in the capitals or main cities of each state (Minsk in Belarus; Moscow and Obninsk in Russia; Kiev in Ukraine); they will focus mostly on the information available centrally. Visits to local hospitals and local institutions will be kept to a minimum since the referral system for cancer treatment is well established and systematized in each of the states. Following the site visits, the last week or ten days of the month will be spent in Lyon to evaluate feasibility and in writing a preliminary report on the visit.

Following the site visits, the final evaluation, the writing of the report and, if feasible, the writing of outline protocols will be carried out in Lyon by Dr Cardis in consultation with the consultants, and with the help of the three advisers from the affected states, who will be invited to spend three weeks to one month at IARC. A draft report will be prepared, reviewed during a meeting of the consultants and temporary advisers, and then circulated to the Epidemiology Study Group as well as to relevant experts in other countries.

The final report will be presented to a meeting of the full Epidemiology Study Group to be held either in Lyon or Rome; this meeting will be open to all interested parties.

PRELIMINARY TIMETABLE

Based on the assumption that a contract can be signed between the IARC and the Council of Europe for the conduct of this feasibility study by 1 May 1992, the timetable will be as follows:

May 1992:

- Recruitment of consultants.
- Identification of temporary advisers.
- Preparation of visits to the affected states

June 1992:

- Finalization of detailed feasibility protocol at IARC by E. Cardis.
- Preparation of visits to the the affected republics

July-August-September 1992:

State-specific review of the feasibility including one-week preparation in Lyon, two-week site visits in one of the affected states, and one-week evaluation and preparation of a preliminary report. Depending on the availability of consultants, this phase may actually be carried out over 4 months (up to October 1992).

October-December 1992:

- Review and evaluation of information collected at IARC, in collaboration with advisers from the affected states.
- Preparation of draft report. Preparation of outline protocols, if appropriate.
- Meeting of consultants and temporary advisers to review draft protocol.
- Circulation of these documents to the Epidemiology Study Group, the Medical Committee of SIEAD/OPA/Chernobyl and other appropriate experts.

End of December 1992:

- Meeting of the Epidemiology Study Group to review the results of the feasibility study.
- Finalization of the report and outline protocols.

Needs in personnel are as follows:

- Dr Cardis, project leader, 4 months
- 6 months of consultants based in Lyon
- 1 half-time secretary (6 months), based in Lyon
- 3 advisers, i.e. 1 each for Belarus, Russia, and Ukraine (2 weeks in their home state, and 1 month in Lyon)
- 1 Special Training Award, part time.

Travel needs:

Dr Cardis, accompanied by two consultants at a time, will carry out one trip to each of the three affected republics. Each trip is expected to last approximately two weeks. Dr Baverstock may join one or more of the site visits.

A temporary adviser each from Belarus, Russia, and Ukraine will travel to Lyon for one month for the preparation of the feasibility report and protocols.

Drs Cardis and Baverstock will meet for two days twice (in Lyon and in Rome), during the course of these months, to discuss progress.

All consultants will spend one week in Lyon at the beginning of the study.

Meetings

- Meeting of consultants and temporary advisers to review the draft report. It will be held in Lyon and will last two days.
- Meeting of the Epidemiology Group at the end of December to present the conclusions of the feasibility study. This meeting will be held either in Rome or in Lyon and will last two days.

List of participants

TEMPORARY ADVISERS

Dr Anssi Auvinen

Finnish Cancer Registry, Helsinki, Finland

Dr Lars Ehrenberg

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Dr Romualdas Gurevicius

Lithuanian Cancer Centre, Vilnius, Lithuania

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University of Tampere, Department of Public Health, Tampere, Finland

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Finnish Cancer Registry, Helsinki, Finland

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REPRESENTATIVES OF OTHER ORGANIZATIONS

Dr Elizabeth Cardis

International Agency for Research on Cancer, Lyon, France

WORLD HEALTH ORGANIZATION

European Centre for Environment and Health, Rome Division

Dr Roberto Bertollini

Epidemiologist

Dr Keith Baverstock

Radiation Protection Scientist

PROGRAMME

Monday, 25 May

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| 08.00 - 09.00 | Registration |
| 09.00 - 09.15 | Opening
- Welcome, scope of the meeting |
| 09.15 - 10.15 | "Estonian Chernobyl clean-up worker cohort and the planned studies"
by Dr M. Rahu, collaboration with the National Cancer Institute. |
| 10.15 - 10.30 | Coffee |
| 10.30 - 11.00 | "Larvian Chernobyl clean-up worker cohort and the planned studies"
by Dr A. Stengrevics. |
| 11.00 - 11.30 | "Lithuanian Chernobyl clean-up worker cohort and the planned
studies" by Dr R. Gurevicius. |
| 11.30 - 12.00 | Discussions |
| 12.00 - 13.00 | Lunch |
| 13.00 - 13.45 | "IARC feasibility studies on Chernobyl clean-up workers" by Dr E.
Cardis. |
| 13.45 - 14.15 | "Second generation studies on Chernobyl clean-up workers' offspring"
by Dr L. Ehrenberg. |
| 14.15 - 14.45 | "WHO European Centre Environment and Health: plans for Chernobyl
clean-up worker studies and their support in the Baltic Countries and
elsewhere" by Dr K. Baverstock and Dr R. Bertollini. |
| 14.45 - 15.15 | "Possibilities of dose reconstruction on the basis of biologic dosimetry"
by Dr A.T. Natarajan. |
| 15.15 - 15.30 | Coffee |
| 15.30 - 17.00 | Discussion on possibilities of collaboration and coordination of study
protocols. |

Tuesday, 26 May

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| 09.00 - 09.30 | "Summary of the current state, identification of the major problems" by
Dr A. Auvinen. |
| 09.30 - 15.00 | Planning of future work. |
| 15.00 | Closure |