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RESEARCH PROGRAMME

S Y N T H E S I S O F R E S U L T S

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PREFACE

The research carried out by the Radiation Protection Programme of the Commission during the period 1981-1984 has been reviewed and evaluated by the Management and Coordination Advisory Committee (CGC) "Radiation Protection" and the services of the Commission. The outcome of the review is presented in this report. It gives a critical synthesis of results achieved and an overview of problems in radiation protection, as well as some essential features of the management of the programme. This review also reflects the progress of cooperation within the Community made in radiation protection research as a consequence of the efforts of the Commission over many years. Radiation Protection remains an issue of great public concern, and it is hoped that this report will be useful in putting the problems into perspective and will thus help the competent authorities in decision making.

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EXECUTIVE SUMMARY

The Commission of the European Communities and the Management and Coordination Advisory Committee (CGC) "Radiation Protection" have prepared a review synthesizing the scientific results of the Radiation Protection Programme obtained during the period 1981-1984. The objective of the programme, the fifth of a series initiated on the basis of the Euratom Treaty, had been to evaluate objectively effects and hazards arising from ionizing radiation and thus to contribute to the protection of man and his environment. Thereby it has

- integrated radiation protection research in Europe and stimulated cooperation in this field, and
- contributed to the scientific background for the Community "Basic Safety Standards for the Health Protection of the General Public and Workers against the Dangers of Ionizing Radiation".

The Radiation Protection Programme corresponds to a significant and relevant share of worldwide efforts to improve scientific knowledge and practice in radiation protection. The programme spanned a wide range of topics and required constant interaction amongst them as well as amongst scientific developments occurring outside radiation protection research. Examples are: Movement of radionuclides in the environment and in man, reduction of man-made exposure including that from medical diagnostics, exposure and effects of natural radioactivity, risk assessment from the nuclear fuel cycle, treatment of radiation accidents, definition of somatic and genetic radiation risks, mechanisms and prevention of radiation-induced cancer.

The 1980-1984 programme had been endowed with a budget of 59 MioECU, including 10 MioECU for the year 1980. In fact, 1980 was an overlapping year between this and the preceding programme. Therefore this report covers the period from 1981 to 1984, only during which time 49 MioECU were spent, mainly in cost-shared contracts. More than 500 projects were executed, in which nearly all relevant national institutions and universities of the Community participated. The impact of these contracts can be seen from about 4.500 scientific publications which appeared during this period. Cost-sharing has been an effective means of attracting interest and funds on the national level, and the Commission covered thus 35-45% of all pertinent research in the Community. About 80% of all such research was associated with the programme by scientific contacts, cooperation and information exchange.

Workshops, symposia, study groups and expert meetings represented an indispensable instrument for cost-efficient cooperation and a large dissemination of knowledge. During the 1981-1984 period, 144 meetings dealing with topical subjects and involving more than 4.000 participants

were organized by the Commission. A total of 66 proceedings of these meetings, or reviews on various aspects of practical radiation protection, have been published during the period considered. Short-term study visits by contractors in other laboratories and grants to young scientists served to strengthen cooperation and to improve training in radiation protection. Relations were also maintained with relevant international organizations and with radiation research programmes of countries outside the Community.

The present synthesis puts these results into the general frame of radiation protection research and allows comparison of different projects dealing with a given problem. Conclusions and recommendations drawn on the basis of the results obtained and of new developments in research have been implemented in the 1985-1989 programme, allowing for continuous adaptation to the changing needs and progress of radiation protection.

Research in radiation dosimetry and its interpretation had the objective to develop and implement new concepts and quantities in radiation protection, to improve radiation protection instruments and dosemeters, to interpret risks in terms of dosimetric quantities and to collect and evaluate basic data for radiation protection dosimetry.

- Attempts were successful in assimilating the concept of effective dose equivalent and in laying down the scientific grounds for the new estimations of dose equivalent recommended by ICRU at the beginning of 1985.

- Individual dosemeters and survey instruments were developed and calibration for neutron and beta radiation was performed. The measurement of plutonium in the lungs of workers was improved. Accident detectors based on human hair, human desiccated tissue, natural and synthetic fibres of clothes were investigated.

- Microdosimetric data were provided and applied for the interpretation of related biological studies with respect to an increase of the neutron quality factor. Experimental studies suggest a larger biological efficiency of neutrons at low doses. Such results have become an important issue since existing human data now appear unreliable.

- New data have been collected, evaluated and published on stopping power, kerma and conversion factors, ionization potential, microdosimetric and secondary particle distributions. Detector materials were investigated which enabled the development of improved personal dosimeters.

Research on the behaviour and control of radionuclides in the environment was performed in order to acquire and improve data on the

behaviour of radiologically significant radionuclides in the environment and to provide models for normal and accidental releases.

- Radionuclides, especially long-lived ones, were followed in the aquatic environment (marine, estuary and freshwater). Binding and remobilisation from sediments have been identified as important mechanisms in the redistribution of radioactivity. Organisms were found which concentrate radionuclides and thus can serve as indicators of contamination.

- Movement of radionuclides in the terrestrial environment depends on the various modes of deposition, soil-plant and plant-animal transfer. Tritium and carbon-14 move readily in the environment and undergo metabolic transformations.

- The transformation of long-lived radionuclides into chemical forms (speciation) resulted in different environmental behaviour.

- Models were improved or developed, and parameters were determined to describe and predict the behaviour of radionuclides after releases during normal operations of nuclear plants, under accidental conditions, or from waste depositories.

Research on short-term somatic effects of ionizing radiation was aimed at understanding the mechanisms of biological action of radiation and at finding means to diagnose and treat radiation accidents.

- Radiation-induced changes in DNA structure have been better defined with respect to lesions induced in purine and pyrimidine bases, the origin of strand breaks and the possibilities of modifying DNA damage by various agents.

- Bone marrow transplantation treatment of victims of radiation accidents with significant over-exposure to large parts of the body has been improved by pretreatment of the graft and by better avoidance and therapy of graft versus host disease. The consequences of late radiation damage to the hemopoietic and immune system have become understood.

- Means for assessing damage and for treating the consequences of accidents involving local irradiation have been ameliorated, and a better understanding has been gained of the dependence of radiation effects on conditions of exposure and radiation quality.

- The developing organism has been studied during its embryonic, foetal and early postnatal stage with respect to its radiosensitivity and the consequences of exposure. The brain was found to be particularly radiosensitive to exposure in utero.

Research on late somatic effects of ionising radiation was carried out with the aim to prevent non-stochastic late damage, i.e. that arising only above a threshold dose, and to assess the risks of cancer, emphasis being given to the risks occurring from incorporated radionuclides.

- Non-stochastic late effects of radiation from accidental over-exposure were studied with respect to the pathogenetic mechanisms involved, threshold doses and the influence of other factors particularly in lung and brain.

- Studies into the molecular nature of carcinogenesis have elucidated the role of viruses and oncogenes in radiation-induced cancer.

- Studies on radionuclide uptake by inhalation and intestinal absorption have dealt with conditions prevailing for members of the general public and of workers and have redefined metabolic models to be used in radiation protection.

- Carcinogenesis from incorporated radionuclides has been studied, particularly in bone and lung, an improved estimate of the risk of bone cancer from plutonium has been achieved.

- Standardization of procedures and training of scientists in late effect studies has continued to be a preoccupation of the European Late Effect Project Group (EULEP) as a basis for cooperation between European institutes.

Research on genetic effects of ionizing radiation had the purpose to clarify basic mechanisms of radiation-induced genetic changes including the basis for individual radiosensitivity, to assess genetic damage arising from radiation exposure and to obtain more realistic risk estimates for genetic damage in man.

- Biochemical mechanisms by which certain hereditary diseases increase radiosensitivity have been detected.

- Tests have been developed to characterize individual radiosensitivity.

- Methods to determine past exposure to radiation and other genotoxic agents have been perfected, particularly with respect to chromosome aberrations in lymphocytes.

- Knowledge of the risk of mutations, translocations and non-disjunction after irradiation of germ cells has been improved.

Research on the evaluation of radiation risks had the objective to develop an integrated approach to evaluate both benefit and risk to man and his environment due to the utilization or presence of ionizing radiation. Results obtained in other sectors were used in establishing comprehensive methodologies for risk evaluation.

- Risks from natural radioactivity (external gamma radiation and indoor exposure to radon and its daughter products) were evaluated and approximate dose distributions for some critical situations and/or regions determined. Parameters and modalities of exposure were studied with a view to developing cost-effective countermeasures.

- Risks from industrial uses of radioactivity were assessed for normal operation conditions and accidental situations, and steps of greatest uncertainty were identified.

- A regional case study to evaluate and compare risks from different sources led to the development of appropriate risk assessment methodologies and to the definition of risk management strategies in view of the optimal use of protection resources.

- Case studies of occupational exposure and optimization of radiological protection allowed further implementation of the ALARA principle.

- Epidemiological data from populations exposed for medical reasons yielded more detailed risk coefficients. Improved methods for risk assessment were developed by feasibility and simulation studies.

- Statistical data on situation and trends in medical diagnostic radiology, on patient exposure and dose reduction were collected to evaluate current radiological practices.

- A more realistic assessment of organ doses from radiodiagnostics has been obtained and some genetically and somatically significant doses have been determined with a view to evaluating trends in population exposure.

- Quality assurance measures in radiodiagnostics have been set up which permit the reduction of patient exposure and which establish better criteria for image quality and for the selection of appropriate procedures.

PART 1. Introduction

1.1. Importance of Radiation Protection Research

Man is exposed to ionizing radiation from many different sources, from medical procedures, from industrial applications and from nuclear power production as well as to natural radiation from cosmic rays and from ambient natural radioactivity. Ionizing radiation was one of the first potentially harmful agents for which basic protection principles were defined, and exposure limits fixed and regularly revised, based on new scientific understanding. Radiation protection was also the area where risk-benefit analysis was first carried out.

Efficient protection of workers, of the public and of the environment requires an understanding of the effects radiation can have. It requires knowledge of the transfer of radioactive material in the environment and from there to man. It needs an estimation of the doses to which man may be exposed and of the risks these may present in relation to the benefits of the peaceful uses of ionizing radiation in, for example, industry and medicine.

The need for research in radiation protection, associated with the development of nuclear power and of other radiation applications, was clearly recognized when the EURATOM treaty was signed, and a first training and research programme was initiated by the Commission. Since this time the programme has been continuously adapted to the changing needs of radiation protection and has

- integrated radiation protection research in Europe and stimulated cooperation in this field,
- provided the scientific background for the "Basic Safety Standards for the Protection of Workers and the General Public",
- contributed to the dissemination of knowledge on radiation protection research,
- aided political decision making on questions of radiation exposure.

Radiation protection research involves a wide range of different subjects and must remain in close contact with a large number of other disciplines. As the years have passed, certain problems have been solved, others have only been recognized during recent years. Radiation protection remains a problem of direct relevance within the larger frame of protecting man and his environment from harmful agents, and includes for example projects in:

Natural radiation, in particular inhalation of radon, which is the principal contribution to the overall population exposure.
Diagnostic radiology, the largest contribution to man-made population exposure.
Radioactive pollution from all categories of sources, tracing its pathways to man.
Effects of low doses which are difficult to determine by direct experimental investigation and their interpretation.
Carcinogenesis, the principal somatic radiation hazard.
Genetic damage, its mechanisms and risks to man.
Accidents, strategies for analysis, prediction of their effects, mitigation of their consequences and countermeasures.
Risk assessment, taking into account both benefits and harm from ionizing radiation, an essential goal of research on radiation protection.
Radiation dosimetry for the protection of workers and the population, its concepts and practical solutions.

1.2. Achievements of the Commission's Radiation Protection Programme

The fifth Radiation Protection Programme was decided for the period 1980 to 1984 on 18 March 1980, with a budget of 59 MioECU. One of the characteristics of this programme was its financial overlapping during 1980 with the previous programme 1976 to 1980. As the budget for 1980 was 10 MioECU, an amount of 49 MioECU remained effectively available for the four years 1981-1984. An important achievement of this programme has been its ability to definitely link research of the Member States in radiation protection together into a coherent network, resulting in an intensive and cost-saving interdependence of European activities in this field. This has proven to be of utmost importance during the last few years of budgetary austerity. While still requiring complete information on all aspects of radiation protection, each Member State can take advantage of the collective knowledge and facilities of the others and no longer needs to set up expensive installations for treatment of accident cases, for marine or terrestrial ecology, for experimental exposure of animals to radionuclides, to mention but a few examples.

A few specific achievements from more than 500 projects carried out during 1981-1984 demonstrate how successful this multidisciplinary cooperation of all relevant institutions and universities from Member States has been:

- It is often not realized by the public that natural radiation accounts for some 70 to 80% of the total radiation exposure to the population, about half of it being due to radon and its daughter nuclides which emanate from the ground and from construction materials. This exposure which essentially affects the lung, and might cause lung cancer, depends on the degree to which radon is diluted after release and is e.g. influenced by apparently unrelated factors: radon exposure increases if, to conserve energy, insulation of houses is improved and thereby air exchange is

reduced. The definition of the different factors affecting radon concentrations and their measurements have been standardized and natural radioactivity in construction material is being studied. Sampling exposure data in houses under different conditions in the Community have allowed the assessment of the relative risks in a much more comprehensive way than would have been possible on the basis of limited data from one member state only. This data form the basis for rational decisions to reduce such exposure where necessary.

- Medical radiodiagnosis involves a large part of the population and gives in many instances significant doses to the individual. Surveys have therefore been organised on a national level to study working practices, equipment functioning and patient exposure. Based on these results work on the elaboration of criteria for quality assurance for several radiodiagnostic procedures has been initiated. Suggestions for improvements and changes resulting from this new knowledge will certainly take some time before they are generally applied in practical medicine but will eventually contribute to avoid unneccessary patient exposure.

- Radiation protection dosimetry must be based on dosimetric quantities which can be measured and can be related to the primary limiting quantities such as effective dose equivalent which in principle cannot be measured. The Radiation Protection Programme of the Commission had a large impact on the maturation of the new concept of dosimetric quantities for external radiation recommended by the ICRU in 1984. A unified set of conversion factors of these quantities to effective dose equivalent have been evaluated jointly by several contractors as a first step of implementation into practical radiation protection.

- Microdosimetric interpretation of biological radiation effects of neutrons has much stimulated the still ongoing re-evaluation of neutron radiation quality which resulted in the recent discussion by ICRP to double the neutron quality factor. The re-evaluation is being extended to other radiation modalities and is largely based on microdosimetric analysis of radiobiological data. A possible increase of the quality factor of neutrons will have a considerable impact on the development of new radiation protection instruments.

- Tritium, a natural radioactive hydrogen isotope, is also produced by nuclear fission. It will become even more important as nuclear fusion is developed, although it is not particularly toxic. Tritium readily spreads through the environment as tritiated water and also as organically bound tritium and can thereby enter the human food chain. Several European institutes supported by contracts of the Commission cooperate on this problem. Among them are the only two European institutions where radionuclide metabolism can be

studied in farm animals: the results of this expensive research project are available to all Member States.

- Radionuclides released into the aquatic environment can be transferred through algae, shellfish and fish and eventually reach man. An understanding and prediction of their behaviour is required to assess the impact, not only of nuclear industries, but also of conventional ones. Model transfer studies are made on the situations along the Rhone and the Meuse, two European rivers with different ecological characteristics along which many such industries are located.

- Accidents involving local irradiation of skin and underlying tissues are not life-threatening but can lead to long-term serious consequences. The treatment of such accidents poses problems for clinical management and rehabilition. Dosimetry, reconstruction of the accident and clinical information are required to decide whether skin transplantation or conservative treatment are best suited. The risks for late effects such as deep ulcerations, keloids or cancer must be assessed. Specialized facilities for such patients have been developed.

- The radiosensitivity of a human population is not uniform. In addition to a few people with hereditary diseases who are especially sensitive to radiation, a certain limited variability in sensibility in the population has been demonstrated. The extent and reasons for the variability of radiosensitivity are being investigated in a coordinated way by several laboratories. Cooperation in this field is crucial because the techniques to define radiosensitivity must be standardised.

- Cancer is a possible somatic hazard of an exposure to low doses of ionizing radiation. The study of radiation-induced cancer involves a multifacetted approach based on an understanding of radiation-induced changes in nucleic acids, molecular biology of oncogenes and viruses, large scale long-term studies following external irradiation or internal exposure to radionuclides and epidemiological observations in man. Cost efficiency has been achieved in this field, based on close coordination and cooperation between different research teams.

- Activation of certain genes, the oncogenes, has recently been recognised to be a fundamental process in carcinogenesis. Radiation protection research has both benefitted from and contributed to this progress. These studies require special knowledge in molecular biology and in modern methods of DNA and virus research and cooperation with specialized laboratories is imperative. First results have been obtained on three principal targets for such oncogenes that are actually under study, radiogenic osteosarcoma, breast cancer and leukaemia.

- Epidemiological investigations provide crucial human data for risk assessment. An important study supported by the Commission since 1968 deals with the consequences of thorotrast exposure. This material, used as X-ray contrast medium from 1929 until 1950, was found to induce liver cancer, liver cirrhosis and leukaemia. Another study deals with the late consequences (osteosarcoma, bone lesions, other tumours and kidney and liver damage) of radium-224 given to man for therapeutical reasons. The information available from these investigations has contributed substantially to the assessment of the risk of cancer from radionuclides deposited in liver or bone. Correct planning, harmonisation of methodology and interpretation are all-important for such epidemiological studies which deal with small groups of people and which are extremely expensive to perform due to the long time needed to get valid results.

- The probability of severe radiation accidents is very low and many uncertainties enter the analysis and prediction of their consequences. This makes it imperative to develop uniform methodologies for their evaluation. The collaboration of scientists working in different fields (e.g. atmospheric dispersion, food chain transfer, dosimetric models, socio-economic impact) has made it possible to deal with all relevant aspects of a global overall methodology and for other laboratories, not having all the required facilities, to gain access to the know-how and computational models developed for such analysis.

It should be pointed out, however, that the interest of much of this work is not restricted to radiation protection proper, but often has important spin-offs in other fields such as:

- Bone marrow transplantation, developed in order to be able to treat victims of radiation accidents with significant over-exposure of large parts of the body has enabled radiation therapy combined with bone marrow transplantation to become a useful treatment for leukaemia and certain other hematological disorders, especially in children.

- Toxic substances in the environment move according to the same laws as do radionuclides although they are usually much more difficult to detect. Models elaborated for the prediction of the consequences of discharges from nuclear industries, from waste disposal or for the management of accidental releases are therefore pertinent also to describe the behaviour of other toxic products.

- The increasing awareness of the presence of carcinogens in the environment makes their rapid detection imperative. Methods to recognize potential carcinogenes have been elaborated on the basis of studies on repair of radiation damage, and techniques to monitor chromosome aberrations in

persons exposed to toxic agents were first developed for the purpose of radiation protection.

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The results from each of the contracts are summarized in the "Progress Report 1980-1984"(1) of the Radiation Protection Programme (EUR 9733) and published in detail in some 4.500 publications, which were the subject of a review and refereeing session of the CGC in October and in December 1985. Members of the CGC and staff of the Commission prepared evaluation documents for each of the six sectors of the programme, which are now assembled in this "Synthesis of Results" of the Radiation Protection Programme 1981-1984.

A comparison of this synthesis with the one for the previous 1976-1980 Radiation Protection Programme demonstrates clearly the capability of the programme to adapt to new developments in radiation protection and to new priorities. The evolution of the sector "Evaluation of radiation risks" is in itself an example. Especially the areas of natural radiation and medical diagnostics deserve mentioning here. Other areas are only beginning to develop, such as cell transformation studies and studies on the developing organism. Research of uncertain outcome is, however, still very restricted. Certain areas of former high priority in which valuable results were achieved, need in many cases continuation of support at a lower level only, sufficient to maintain the necessary pertinent competence in the Community. For instance, during more than two decades high priority was given to the treatment by bone marrow transplantation of people who might be severely irradiated in an accident and contractors achieved excellent results. Presently, emphasis has shifted to local irradiation treatment, and this was strengthened in the 1985-1989 programme.

1.3. Present State of the Programme

A new pluriannual Radiation Protection Research Programme 1985-89 has been approved by the Council of Ministers on March 12 1985 and has been budgetted with a sum of 58 Mio ECU. This money is being spent on:

- Cost-shared contracts with national institutes and laboratories: up to now a total of more than 300 projects have been selected from 500 applications.

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(1) As mentioned already above, the year 1980 was an overlapping year of the two programmes 1976 to 1980 and 1980 to 1984. New contracts and projects were prepared during 1980 to begin on 1 January 1981. Therefore all results and figures in this report refer to the period 1981-1984.

- Organization of cooperation between European laboratories by means of study groups, workshops, intercomparison programmes.

- Diffusion of knowledge in radiation protection research by means of publications on suitable subjects, conferences with the participation of scientists from European and other countries.

It might be useful to describe in the following pages the areas of high priorities for the period 1985-1989, in order to compare them with the execution of the programme 1981-1984. This should enable a detailed evaluation of the value and importance of the Radiation Protection Programme and the evolution it must undergo.

- Radiation dosimetry and its interpretation

  The implementation of new concepts and quantities introduced into radiation practice by ICRP and ICRU, recent preliminary discussions of ICRP to recommend a twofold increase of the neutron quality factor, as well as the application of the Commission's Basic Safety Standards rely on a continuing reassessment of scientific and technological development in dosimetry.

  Personal dosimetry and area monitoring will be improved, particularly for neutrons and low energy beta- and photon radiation, by further developing dosemeters and continuing calibration and intercomparison programmes. Dosimetric methodology as well as physical and biological dosemeters will be further developed for inhomogeneous exposure, in order to improve the evaluation of the dose received by different organs of the body in case of accidental irradiation.

  Based on microdosimetric studies on the interaction of radiation with biological tissue, a more reliable extrapolation from high to low doses may be made, and a theoretical basis for a final revision of the quality factor for neutrons may be obtained.

- Behaviour and control of radionuclides in the environment

  Comprehensive information on the behaviour and control of certain radionuclides will be used for the assessment of radiation risks. Emphasis is placed on those processes through which radioactivity can reach man after long delays or after accidental releases.

  Natural radionuclides may spread through surface and ground water following release via the mining and milling of ores containing high levels of natural radioactivity, and the

factors involved as well as the possibilities for preventive measures are being investigated.

The environmental long-term and long-distance impact of radionuclides discharged under controlled situations is affected by their chemical speciation in the environment and their bioavailability. This involves studies mainly on actinides and on globally distributed tritium and carbon-14.

Dynamic models for the prediction of the behaviour of radionuclides in air, water and soil following possible accidental releases, and for the initiation of countermeasures are being refined by characterizing critical pathways and assessing parameters and their uncertainties under realistic conditions.

- Non-stochastic effects of radiation

The aim of research is to prevent and treat accidental, especially local overexposure. Emphasis is given to those tissues most likely to be involved and undergoing severe damage, i.e. the skin, hematopoietic-immune system, thyroid and the developing organism.

Models are being developed to define threshold doses under different exposure conditions. The critical temporal and biological factors of the actions of radiation on early organ and human development, e.g. in utero, are being studied, this includes particularly the central nervous system.

- Radiation carcinogenesis

Radiation-induced cancer is considered to be a possible somatic hazard of low dose exposure. It is studied by a balanced approach in which epidemiology is backed up by selected cellular and animal investigations.

In vitro transformation systems relevant for the human situation are being developed further to obtain information on low doses and high LET radiation. Models for human radiation-induced cancer are being investigated, particularly with respect to the influence of radiation quality and of age.

The relation between deposition of incorporated radionuclides and target cells is being studied in lung and bone, and possibilities for decorporation are being investigated. Models for radionuclide behaviour are being refined taking into account physical and chemical characteristics of the radioactive material, as well as age, and biological variability.

Epidemiological studies on human populations exposed occupationally, accidentally or for medical reasons are being

continued in order to obtain reliable data for risk assessment for man.

- Genetic effects of ionizing radiation

The aim is to gain more insight into the relationship between radiation damage and genetic effects, to have available methods to detect variations in individual radiosensitivity and indicators for genetic damage, and to obtain a better assessment of genetic risk in man.

Biochemistry and genetics of radiation sensitivity and repair as well as the relationships between DNA repair and pre-mutational or pre-carcinogenic events are being studied to understand the reasons for variations in human radiosensitivity. Methods are being developed to detect and score on a large scale radiation-induced genetic effects in human somatic and germ cells.

Methods are being improved to assess genetic damage in persons exposed to radiation, particularly when this occurs in an inhomogeneous way and over long periods of time.

Models and experimental studies are being developed to verify the validity of the methods used in risk assessment, particularly in extrapolation of data from somatic to germ cells, from animals to man and from high to low doses.

- Evaluation of radiation risks and optimization of protection

The main feature is an integrated approach to evaluate the risks from the nuclear fuel cycle as well as those from other radiation sources, such as natural radiation or medical diagnostic radiation. The goal is to optimize radiation protection at all levels.

Exposure to natural radioactivity, the principal contributor to population exposure, may require appropriate countermeasures in the future. Therefore exposure parameters and modalities such as radon exhalation, aerosol characteristics and air exchange, are being investigated.

The risks from the industrial use of radioactivity are being evaluated on an European scale in a common accident consequence assessment framework using probabilistic risk evaluation methods. This provides a basis on which comparative risks of different energy production cycles can also be assessed to serve as an input for overall decision making.

Optimization of the radiological protection of workers and the public and the further implementation of the ALARA principle remain a basic issue. Decision-aiding techniques other than cost-benefit analysis have to be applied to rank different protection options.

Approximately one radiological examination per person per year on average is the major source of man-made population exposure. To avoid unnecessary exposure, the radiological practices are being optimized by establishing quality assurance criteria, by determining doses from the various techniques and by improving the selection criteria of the diagnostic procedures. This is needed for the practical implementation of the "Council Directive on Radiation Protection of Persons Undergoing Medical Examination or Treatment".

PART 2. Results of Sectors

SECTOR A

RADIATION DOSIMETRY AND ITS INTERPRETATION

1. Purpose and General View

2. Development and Implementation of New Concepts and Quantities

   2.1. New Quantities
   2.2. Implementation of Physical Quantities for External Radiations
   2.3. Intercomparisons of External Radiation

3. Development of Radiation Protection Instruments and Dosemeters

   3.1. Survey and Area Monotoring Instruments
   3.2. Individual Dosemeters
   3.3. Accident Dosimetry
   3.4. Dosimetry of Internal Exposure

4. Interpretation of Risks in Terms of Dosimetric Quantities

   4.1. General Remarks
   4.2. The Problem of the Quality Factors
   4.3. RBE of Densely Ionizing Radiation

5. Collection and Evaluation of Basic Physical Data for Radiation Protection Dosimetry

   5.1. Stopping Power and Phase Effects
   5.2. KERMA Factors and Neutron Transport
   5.3. Concepts, Methods and Data of Microdosimetry
   5.4. Concepts and Data for Dosimetry of Incorporated Radionuclides
   5.5. Charged Particle Tracks
   5.6. Research on Detector Materials for TLD

6. Perspectives and Recommendations

1. PURPOSE AND GENERAL VIEW

The limits and standards for the control of exposures of both workers and the general public to ionizing radiations and radioactive materials are described in terms of dosimetric concepts and quantities; hence it is the physical dosimetry that links together biological investigations in the different sectors of the Radiation Protection Programme. The objectives of research in dosimetry are therefore to ensure

- that instrumentation and methods are available for a coherent application of the Basic Safety Standards embodied in the EURATOM Directive within the Community;
- that relationships between the physical dosimetric quantitites and biological effects are correctly understood;
- that this understanding finds acceptable interpretation in the quantities used for practical radiological protection.

The work in this sector was consequently directed towards the development and implementation of conceptual quantities for use in radiological protection, the development of instruments for the measurement of such quantities, the development of theoretical understandings of the relationships between physical quantities and biological effects, and the interpretation of radiation risks in terms of these parameters. There is also, of course, work on the determination of basic physical data as are required for these developments.

2. DEVELOPMENT AND IMPLEMENTATION OF NEW CONCEPTS AND QUANTITIES

2.1. New Quantities

The concept of effective dose equivalent is the basis of limiting exposures under the terms of the Euratom Directive. Methods for its direct assessment or surrogate assessment in terms of secondary quantities are still a matter for debate. In 1981-1984 a number of attempts were made to assimilate this quantity into the practical monitoring of external radiation. It must be noted that it was only at the beginning of 1985 that the International Commission on Radiation Units and Measurements (ICRU, Bethesda, 312) (1) produced recommendations as regards estimators of dose equivalent for practical monitoring. The ICRU report committee was working on the development of these recommendations during the whole period 1981-1984 and contributions from contractors and research work of the Commission's Radiation Protection Programme were an important input to their deliberations.

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(1) For a detailed list of contracts cited see Annex III

As one contribution to the formulation of the ICRU recommendations, dose distributions in tissue-equivalent spheres, which have for some time been under consideration as a basis for the specification of secondary quantities, were investigated both experimentally and theoretically. Efforts were made (NRPB, Chilton, 308; PTB, Braunschweig, 284) to investigate by experimental methods dose distributions in both spherical and cubic tissue equivalent phantoms. The latter form was investigated because it might have practical advantages for calibration purposes.

In parallel with these studies and in preparing the new ICRU concepts theoretical studies based on the development and use of Monte Carlo techniques were carried out (PTB, Braunschweig, 284; GSF, Neuherberg, 287 and 458) to determine the relationship between possible secondary dose-equivalent quantities and effective dose equivalent. A necessary part of these latter developments was the computer specification of appropriate male and female phantoms. One effect of this work is an increased confidence in the ability of computational methods to predict three-dimensional dose distributions in complex objects such as the human body. A possible consequence is that computational methods may now be used to provide conversion factors from radiation field quantities such as air kerma and neutron fluence to both primary and secondary dose quantities rather than resorting to the direct implementation of the latter quantitites in the form of physical standards. This work also contributed to the basis for a new family of operational quantities (ICRU, Bethesda, 312) which will be used for the specification of monitoring instruments for external radiation.

2.2. Implementation of Physical Quantities for External Radiations

Although it was shown that for neutron and photon radiations it is possible to base secondary standards of dose equivalent on computation, it seems likely that it will be more practical for beta radiation to develop real physical standards because of the complexities introduced by the actual construction of beta sources. Work towards this goal (NRPB, Chilton, 308) has resulted in the design and construction of an extrapolation ionisation chamber surrounded by sufficient material to simulate the backscattering of the human body.

For photon and neutron radiations it is important to provide accurate primary radiation field standards of air kerma and neutron fluence over a wide range of energies for calibration purposes. One area where these standards have been lacking is for neutrons in the energy range from a few keV up to about 100 keV. Joint work (PTB, Braunschweig, 502; NPL, Teddington, 506) has established the reaction of protons with Sc-45 as a possible accelerator source for neutrons in this energy range. This is a valuable supplement to filtered reactor beams whose spectra were further characterised during the period (PTB, Braunschweig, 291).

It is very helpful to have available broad neutron calibration spectra which simulate irradiation conditions in practical radiation protection work. Furthermore, there are neutron dosemeters which can not be calibrated in mono-energetic neutron beams and need broad neutron spectra for their calibration. Several such neutron sources were developed and their spectrum carefully analyzed (CEA, Saclay, 524). A sensitive neutron spectrometry system was developed for the neutron range of a few keV to about 1 MeV (UKAEA, Harwell, 305). This system is to be used to investigate the spectra in operational situations where neutrons in this energy range are believed to contribute significantly to doses of workers.

Some investigation was made of the possibility of using a multi-detector system made of several individual dosemeters for the better derivation of the effective dose equivalent for individuals (PTB, Braunschweig, 291). This is of particular importance in radiation protection situations of non-isotropic and time dependent radiation fields. This problem is increased to some extent by the current uncertainty as regards the quality factors for neutron radiation introduced by recent ICRP statements (see page 13-14).

2.3. Intercomparisons of External Radiation

Of particular importance to radiobiology and radiotherapy is the comparison of dose measurements between different centres and institutions (EULEP, 390; TNO, Rijswijk, 525). Activities in this area were rewarded by a considerable reduction in the divergencies between participating institutes which for neutron radiations resulted in a reduction from a mean spread of about 7%, with a few participants as much as 20% different from the mean, to a mean spread of about 3% with a few giving 5% differences. In the case of the X-irradiation of mice a comparison showed that the majority of participants were within 5%, but some made dose estimates that were as much as 30% divergent from the mean. Attempts are being made to account for and resolve these differences.

For the investigation of environmental exposure at reactor sites, the intercomparison of thermoluminescence dosimeters at environmental radiation levels is of particular importance. Two such intercomparisons were carried out (NRPB, Chilton, 501) each with five participating laboratories. The mean uncertainty was about 5% for both rounds, however, the results from two laboratories clearly indicated an overresponse to low energy photons and stimulated these participants to re-examine and change their dosimetry systems, resorting to LiF dosimeters rather than using dosimeters based on high sensitivity materials.

3. DEVELOPMENT OF RADIATION PROTECTION INSTRUMENTS AND DOSEMETERS

In radiological protection dosimetry, low energy neutrons still require particular attention not only because of difficulties caused by the cut-off in sensitivity of currently used detectors but also due to the fact that neutrons in the energy region between 0.1 and 1 MeV have the largest biological effectiveness . This has maintained a continued demand for the development of radiation protection instruments for area monitoring and personal dosimetry of neutron-gamma fields, as is reflected in the Symposia on Neutron Dosimetry organized by the Commission and the GSF, Neuherberg, in 1981 and 1984 (see Annex V). An improvement of the instrumentation, the data processing and the calibration methods in radiation protection monitoring has to be related to possible changes in operational quantities and quality factors.

3.1. Survey and Area Monitoring Instruments

In practical working-area monitoring of neutrons, "remmeters" based upon the use of a neutron moderator are still very common. These instruments are useful over a wide range of energies, but tend to be inaccurate at very high or low energies. They also are quite heavy because of the amount of moderator required. There is an obvious need for survey meters with an isotropic and correct response in terms of dose equivalent for the measurement of low neutron dose rates sufficient combining sensitivity and discriminating abilitites for low and high LET radiation. They have to be light weight, simple and reliable to operate for practical purposes.

A number of prototype instruments have been constructed in the last five years. Most of them have been based on the low-pressure tissue equivalent proportional counter with which it is possible to measure simultaneously neutron and gamma doses and which can be calibrated to estimate effective dose equivalent directly. The technical development of these counters was coordinated (EURADOS, 507) and was discussed at a workshop "The Practical Implementation of Microdosimetric Counters in Radiation Protection" organized at Homburg in 1984 (see Annex V). This workshop concluded that tissue equivalent proportional counters are capable of measuring dose equivalent in mixed neutron gamma fields with sufficient certainty and accuracy for radiological protection although performance tests are required to gain experience in their use and for comparison with other instruments.

The Jülich Counter (KFA, Jülich, 288) has reached a state of development that is promissing for its extended use as area monitor. The wall thickness has been optimized by transport calculations to match the desired response in terms of dose equivalent. It is possible to measure a neutron dose rate of 1 μSv/h with a precision of better than 20% for neutrons between thermal energies and 20 MeV. In the case of fast neutrons above 0.3 MeV it provides an effective discrimination between gamma

rays and neutrons and for the whole energy range an indication of low and high LET fractions of absorbed dose and dose equivalent. Another compact tissue equivalent proportional counter system is CIRCE (CEA, Fontenay-aux-Roses, 433) which is capable of measuring dose equivalent, absorbed dose and effective quality factor in mixed radiation fields. The dose equivalent index H_I can be provided directly by measurements with CIRCE in a 30 cm tissue equivalent phantom. The commercial LET-2 counter has been associated with a compact and portable pulse-height processing unit by which it is possible to measure a dose equivalent rate of 10 μSv/h (CEA, Grenoble, 293). This counter was used to measure the mean quality factor of neutrons between 0.1 and 15 MeV.

Correlations between the quantity measured with tissue equivalent proportional counters and quantities required for radiation protection have been studied systematically for the whole range of neutron energies encountered in practice and for neutron-gamma fields (KFA, Jülich, 288; Univ., Homburg, 289 and 482). Further, the consequences of the need to convert the complex experimental method into a simple procedure suited for routine dosimetry has been investigated (Univ., Homburg, 482). The close correlation between instrumental response and dose equivalent could be useful in establishing an experimental calibration standard for dose equivalent quantities. The work also included investigations on the application of tissue equivalent proportional counters for accurate absorbed dose measurements in comparison with calculations which simulate the measurements. The resulting over-all uncertainty in the measurement of absorbed dose has been estimated to be 5%. Based on the experience obtained from these studies a prototype of an area monitoring instrument with diagnostic capabilitites is under construction (Univ. Homburg, 482).

Other types of portable monitoring instruments have been investigated in the programme, for example studies of the use of uranium-235 fission chambers as dedicated environmental monitors for nuclear power plants (CEA, Fontenay-aux-Roses, 292). A prototype has been constructed based on a fission chamber of 100 electrodes and 5 of these chambers have been combined to a multidetector system capable of measuring dose rates between 0.2 and 100 mSv/h.

Ionisation chambers were also investigated (TNO, Rijswijk, 302) with an emphasis on small size and high pressure. Such chambers would be useful for measurements both in phantoms and in connection with radiobiological experiments. One interesting aspect of the investigations was the use of different gases and gas mixtures and a study of the influence of the LET of the radiation on the degree of initial and columnar recombination. This work suggests that by the use of different gases and pressures some information about the quality of the radiation may be obtained.

Studies were made of the abilities of commercial Geiger-Müller monitoring instruments and ionisation chambers to measure

suggested secondary dose equivalent quantities for photons (PTB, Braunschweig, 284; NRPB, Chilton, 308). Both institutes concluded that Geiger-Müller counters have a good potential for measuring a quantity proportional to that now recommended by the ICRU. They also found that it would be possible to adapt ionisation chambers by comparatively simple means for use as secondary standards for dose equivalent. Some effort was also given to investigating the influence of environmental factors on the response of the instruments.

The influence of beta radiation on the response of radiation protection instruments has been studied systematically for three instruments (CEA, Grenoble, 523). The maximum energy for the beta radiation has been in the range 0.2 - 2.3 MeV. Different source configurations and source-detector distances have been used to obtain practical guidelines, especially when errors arise in the case of non homogeneous irradiation situations such as low beta energy radiations or small source to detector distances.

3.2. Individual Dosemeters

Soft beta radiation can be detected sucessfully by the use of exoelectronic emission dosemeters. They consist of an oxidized beryllium layer with an extremely high sensitivity even at very low-energy beta radiation (Univ., Giessen, 503; CEA, Fontenay-aux-Roses, 505). It is concluded that the thermally stimulated exo-electron response is independent of electron energy in the 200-700 keV range and linearity is obtained from 10 μSv to 10 Sv. The more advanced beryllium oxide thin film dosemeters developed recently do not suffer from the water absorption problems previously exhibited by dosemeters of this material. The thin film dosemeters are inherently surface specific with a sensitive layer of only about 10 nm.

A working group (EURADOS, 507) has prepared five documents (to be published) which review the state of the art in thermoluminescent dosimetry. These reports deal with annealing procedures, discriminating dosemeters, different read-out systems, personnel monitoring in the CEC and the relative tissue-kerma sensitivity of thermoluminescent materials to neutrons.

In individual neutron dosimetry it is often recommended to use a combination of at least two detectors to cover a sufficiently broad neutron energy range, but there remain a gap between 20 keV and several hundred keV where no optimal detector so far has been available. Significant progress has been achieved in closing this gap by electrochemical etching of CR-39 (polyallyldiglycolcarbonate) foils (ENEA, Casaccia, 299; UKAEA, Harwell, 305). Electrochemical etching greatly increases the size of the tracks allowing easy detection of even recoil hydrogen ions. By controlling the electrochemical etching parameters such as temperature, electric field, chemical solution and frequency it is possible to drastically change the detector response. In this way it is possible to obtain large and uniform track sizes from about 20 keV to 20 MeV neutrons, flat energy response in the

entire energy range of interest and neutron energy response with different thresholds useful for neutron spectrometry. The dosimetric characteristics of commercially available CR-39 plastic detectors have been improved to provide better homogeneity and fewer surface defects so that a lower background can be achieved.

Work was also performed on the polymer development of CR-39 (Bristol University, 564) and much effort has been spent on the investigation of the kinetics of polymerisation. Although progress has been achieved, in particular with regard to measuring the monomer concentration as a function of reaction time using infra-red spectroscopy, more research into the polymer chemistry of CR-39 is needed in order to fully understand the track response and factors governing the reproducibility of the material. The response of the Bristol dosemeter was investigated for isotropic and normally incident neutrons and was found to be closely correlated to dose equivalent for neutron energies between 0.1 and 15 MeV.

The results obtained for this and the ENEA and UKAEA detector systems are fairly encouraging and therefore the combination of an albedo detector and a CR-39 detector seems to provide a solution to the problem of personnel neutron dosimetry although additional information is still required on the neutron spectrum for an accurate assessment of dose equivalent.

Above neutron energies of 100 keV, CR-39 itself can be used as a neutron spectrometer (Univ., Bristol 564). The device principally operates as a proton recoil detector, the recoils originating either in an adjacent radiator or the CR-39 itself. Deconvolution calculations have been tested successfully for various neutron energies and angles of incidence.

The elecrochemical etching process is particularly convenient for short range alpha particles in CR-39 detectors and make these detectors suitable for radon dosimetry as well as in the assessment of individual exposure to radon daughters (ENEA, Casaccia, 299) (see Sector Evaluation of Radiation Risks).

The CR-39 plastic has together with other polymers been used for dosimetry studies using the electret effect, where the electret depolarization created by a high voltage in a sample is used for monitoring the radiation field (Univ. Toulouse and Limoges, 296). The method has to be developed further for reproducibility. It is attractive for radiation protection dosimetry with a sensitivity better than 0.1 mSv and the accuracy better than 10% for X-rays. Furthermore, the initial information is not destroyed by the readout system.

The development of a new thermoluminescence dosemeter covering two neutron energy regions below 0.5 eV and the range 0.5 eV to 10 keV has been finished (CEA, Fontenay-aux-Roses, 292) and brought into service in 1985, after having been successfully

exposed to different sources under the "Joint American-European Personnel Monitoring Intercomparison 1982".

Also studies of track-detectors as cellulose nitrate (CN-85, CR-115) have been initiated (CEA, Fontenay-aux-Roses, 292). Optimum etching of cellulose nitrate is not so straightforward as polycarbonate, environmental effects are more important, and batch to batch variations are more significant. By using boron in the film it is possible to increase the sensitivity to low energy neutrons by a factor of 4. The CN-85 detector has also been investigated by calculations of the theoretical sensitivity of the dosimeter to fast neutrons (Univ., Toulouse, 295) and the applicability as individual dosimeter seems promissing but further studies are needed for this newer material.

Another dosemeter studied (CEA, Fontenay-aux-Roses, 522) has an ability to measure neutron dose for energies of above 100 keV. This is a photographic emulsion in which the amount of remaining silver is measured by fluorescence or by an activation technique.

3.3. Accident Dosimetry

In the case of an accidental radiation exposure it may be important to deploy a physical or biological accident dosimetry method to assess respectively the dose equivalent received by the individual or the induced biological radiation detriment.

Since the cotton fibres of working clothes seem to be a possible detector material for an accident dosimetry system, the phenomenon of exo-electron emission from cotton and its suitability as a dosemeter using exo-electron emission by thermostimulation (TSEE) was investigated (CEA, Fontenay-aux-Roses, 483). It has been found that the phenomenon of TSEE from cotton is very complex. It depends on many environmental and treatment factors experienced by the cotton and thus TSEE of cotton is inappropriate as an accidental dosimetry system.

In pursuing this investigation, it was also found, however, that electron paramagnetic resonance of clothes could be used for the development of an accidental dosimeter (CEA, Fontenay-aux-Roses, 483). Feasibility studies with several types of natural and synthetic fibres were successful. A sensitivity of less than 1 Gy and linearity up to 100 Gy were demonstrated.

In another investigation (Univ., Aberdeen, 310), desiccated human tissue and human hair were studied as possible accident detectors when using the lyoluminescence of these materials. However, efforts to identify human tissues in which the free radicals are sufficiently stable to warrant their study by the lyoluminescence technique were not successful. When analyzing this problem by electron spin resonance, it was found that the decay time of the signals was too short (between 1 and 100 hours) to permit useful measurements in practical cases. Human hair signals were much

more stable, however, the detection limit for hair was found to be 10 to 12 Gy and thus too high for accident dosimetry.

Biological dosimeters such as chromosome aberration counting and biochemical parameters are described in Sector Short-Term Somatic Effects of Ionizing Radiation.

3.4. Dosimetry of Internal Exposures

Major difficulties are presented by the need to evaluate the committed effective dose equivalent due to intakes of actinide elements, particularly of inhaled plutonium dusts. Methods of improving the response of detector arrays for the measurement of plutonium in the lungs of workers have been investigated (UKAEA, Winfrith, 380). This has led to the employment of arrays of phoswich detectors with background estimates derived directly from the subject under investigation, rather than through resorting to separate phantom measurements. This method was combined with computer modelling of the subject's lung geometry. The work is promising but there are still some problems to be overcome and further investigation is required for the estimation of non-homogeneous distributions of plutonium in the lungs. In principle, xenon proportional counters should be better than phoswich detectors for plutonium in lung measurements. The detailed development work of a multiwire xenon proportional counter (UKAEA, Harewell, 434) has highlighted the difficulties in obtaining the expected performance from these detectors and should enable their true potential to be realised.

The finer detail of the dosimetry of alpha particle activity in the lungs is important for understanding the risks to workers with actinide elements and to the general population from the inhalation of radon daughter products from the natural environment. A more precise lung dosimetry of radon daughter products is also relevant to the derivation of alpha particle quality factors when considering the increased incidence of lung cancer in uranium miners (Polytechnics of the Southbank, London, 544; PCL, London, 381). In particular this work has indicated that differences of as much as 50% in the derived doses may result from the neglect of the details of lung morphology between man and animals, of range straggling, and of the phase differences in stopping power. Detailed information on alpha particle dose in the human lung was obtained using microtome sections loaded into CR-39 (Univ., Bristol, 564). This method was used with lung and bone sections to evaluate the relative levels of Po-210 and the total alpha activity for different population groups. Further, studies were started on the microdistribution of Ra-226 and Ra-224 in mouse and beagle dog bone.

4. INTERPRETATION OF RISKS IN TERMS OF DOSIMETRIC QUANTITIES

4.1. General Remarks

During the previous research period there has been substantial progress in the clarification of basic quantities for radiation protection. The introduction of the effective dose equivalent and its almost general acceptance as the reference quantity in radiation protection, both for internal and external radiation sources, have been the expression of the transition from a limitation system to an assessment system for stochastic effects. Although there are still justified doubts whether the ultimate purpose of an assessment system, the derivation of reliable, realistic numerical values of the risk factors at small doses, can ever be reached, there has been significant progress in the understanding of the stochastic effects of small doses of different radiations. The studies of radiation biology and radiation physics within the European Community's Radiation Protection Programme have contributed to this process.

The necessity of the research programme has also been confirmed by new questions concerning the relative biological effectiveness of sparsely and densily ionizing radiations. Considerable uncertainty has been caused due to the fact that the old dosimetry for Hiroshima and Nagasaki has had to be abandoned. The related disappearance of human data on the effects of small doses of neutrons has been accompanied by the emergence of new biological evidence for large RBE values of neutrons. Both issues have increased the need for broad approaches in radiation research which combine a multiplicity of experimental systems and microdosimetric analysis. The symposia on microdosimetry, organized by the Commission in 1980 with the NRPB, Chilton, and in 1982 with the KFA, Jülich, as co-organizers (see Annex V) have again shown to be extremely useful for obtaining such a synopsis of the biological and biophysical aspects of low dose effects and the expressions of radiation quality.

The Problem of the Quality Factors

ICRU has recently defined operational quantities of dose equivalent that are suitable for the routine determination of effective dose equivalent. There is, however, still uncertainty concerning the quality factor, one of the most important ingredients in the numerical definition of the dose equivalent quantities. The recent suggestion of the ICRP to double the quality factors for neutrons is merely an interim step towards a definite revision of the quality factors. The Commission's Radiation Protection Programme will be an important source of information for any such revision.

One aspect of the pending revision of the quality factor is the proposal to replace LET as reference variable by microdosimetric quantities such as lineal energy. Studies on neutron responses of low pressure proportional counters have shown that this is not a

problem of practical importance (EURADOS, 507). However, further data will be required to quantify this point also for other radiation modalities. Some projects of the last research period were concerned with the application of the LET concept as an approximation to energy deposition in small volumes and such results will be relevant to any further analysis of the relative merits of LET and of microdosimetric parameters.

There have been a number of studies oriented towards microdosimetry and its relation to RBE and to risk assessment. Some of these studies were investigating complex systems from epidemiology to large scale animal experiments (Univ. Würzburg, 286; ENEA, Casaccia, 298; TNO, Rijswijk, 375). Others were aimed at cellular studies which could hopefully be extrapolated to expand the risk estimates and the knowledge of RBE values (TNO, Rijswijk, 300; NRPB, Chilton, 413; AERE, Harwell, 306). Further projects such as the experiments with ultra-soft X-rays have been aimed at basic mechanisms and their analysis in terms of microdosimetric data (MRC, Harwell, 412; GSF, Frankfurt, 394; ITAL, Wageningen, 409). Still other investigations were concerned with a variety of biophysical models (AERE, Harwell, 460; GSF, Frankfurt, 394). The common element of all these studies has been the supposition that a large scale comparison of both experimental systems and biophysical models is required to achieve meaningful predictions of RBE and of probabilities of stochastic effects at small doses of ionizing radiations.

4.3. RBE of Densely Ionizing Radiations

Epidemiological studies (see Sector Late Somatic Effects of Ionizing Radiation and Sector Evaluation of Radiation Risks) are an important and directly relevant source of information on RBE, and ultimately also on absolute risk estimates. For densily ionizing radiations the essential information has come either from results of medical or industrial uses of alpha-emitters, or from studies of lung cancer in miners exposed to radon. Their contribution to the general problem of the RBE of densily ionizing radiations is, however, limited because of the complicated problem presented by the spatial distribution of dose. Models of such distributions, especially of radon daughter products in the lung, are still under development inspite of the large amount of effort already invested. In conclusion, statements on quality factors for densely ionizing radiations will have to be based mainly on observations of the effects of small doses of neutrons i.e. of the only densily ionizing radiation which produces approximately uniform radiation fields in the body. But the revision of the Japanese dosimetry indicates that the neutron doses even at Hiroshima were too small to permit a meaningful RBE analysis. The resulting lack of epidemiological knowledge of neutron effects increases the importance of animal studies and cytological investigations.

The results on RBE of densely ionizing radiation are far from definite. Improvement is needed particularly with regard to the following problems: - few studies have yet reached doses that are

sufficiently low to be directly relevant to radiation protection, - in many results there is a lack of numerical estimates of uncertainty, - even the mathematical methods to achieve such estimates are still incomplete, apart from the actual biological or epidemiological uncertainties. The choice of mathematical models in epidemiology and in experimental studies is closely connected to this last problem.

A large mouse experiment was performed with the analysis still being continued (ENEA, Casaccia, 298). Their RBE values are high at doses around 10 mGy of neutrons. This agrees with earlier findings for mammary tumours and it is also in line with the life-shortening data from fission neutrons from the USA. Lower RBE values have been obtained in a large scale mammary tumour experiment (TNO, Rijswijk, 375). However, these data pertain to higher doses, or are extrapolations from higher doses. A quantitative comparison will require a thorough analysis of uncertainties.

Particular efforts were made to conduct broad investigations on different systems including specifically cell killing and chromosome aberrations in various cell strains (TNO, Rijswijk, 300). The authors conclude that the RBE's for these end points are similar and similarly low. Differences between cell strains were found to pertain equally to cell killing and to chromosome aberrations. Preliminary studies of cell transformations, particularly techniques for the dermination of DNA fragmentation patterns in irradiated cells without and with transformations and without and with chromosome aberrations, led to the conclusion that these effects are closely linked if not partly identical in their primary mechanisms. Similar experiments, however, resulted in somewhat different results (MRC, Harwell, 412); and it was found that the RBE values for mutations are definitely higher than those for cell killing.

Inferences about basic mechanisms responsible for the cellular effects of different types of ionizing radiations have also been partly divergent. Interpretations of biological data using the concept of a dose dependent reduction of repair rates had later to be corrected. Collaborative efforts (MRC, Harwell, 412; Univ., Göttingen, 570) on chromosome aberrations produced by various photon radiations has led to the finding that recovery times are substantially independent of dose within the dose range of biological interest. This confirmed the prior idea of lesion interactions which are invoked both in the dual radiation action and in the repair misrepair models (GSF, Frankfurt, 394). The microdosimetric simulations and the models utilized in the various groups (AERE, Harwell, 460; GSF, Frankfurt, 394) have motivated collaborative efforts which utilize new microdosimetric concepts. These concepts, such as the proximity function, provide a linkage between more conventional quantities such as LET and the conventional microdosimetric parameters.

There is a need to identify the real differences and equivalences of seemingly divergent models. Some studies of the underlying

mechanisms (GSF, Frankfurt, 394) seem particularly useful for providing tests for models. They indicate two types of mechanisms with different RBE values. Similar conclusions are based on some evidence of low RBE values for repair deficient cells and high RBE values for cells with normal repair (MRC, Harwell, 412). It was concluded that a study of the high RBE values may be most relevant for radiation protection. One could, however, argue that the low RBE's in repair deficient cells are merely an expression of abnormaly high sensitivities to sparsely ionizing radiations. Individuals with repair deficiencies may then be the critical population at risk from sparsely ionizing radiations and they would seem to deserve more detailed study.

5. COLLECTION AND EVALUATION OF BASIC DATA AND CODES FOR RADIATION PROTECTION DOSIMETRY

The measurable quantities "absorbed dose" and "dose equivalent" are applied in radiation protection as reference quantities of biological effects for the assessment of radiation risk and hazard. For these purposes absorbed dose and dose equivalent must be measured with sufficient accuracy and precision. The availability of physical data such as the average energy per ion pair (W-value), stopping powers, ionization potentials, kerma ratios, conversion factors, interaction and production cross-sections, etc. of appropriate accuracy is thus a basic prerequisite for radiation protection.

Further, dosimetry and microdosimetry are needed to provide a basis for extrapolating and interpreting biological data in order to foster a better understanding of the underlying mechanisms. Since the technical problem of measuring energy deposition to small targets such as DNA has not yet been solved, and possibly never will, this important task of microdosimetry is dependent on computer calculations of charged particle tracks and their energy deposition patterns. Thus, most of this type of work depends on the availability and accuracy of the required interaction cross-sections of charged particles with the atoms of biological tissue. The knowledge of cross sections and energy transfer coefficients in condensed media used in track structure calculations is based on radiation interaction with gases and even these data are uncertain within a factor of 2.

Related investigations on radiation mechanisms are also relevant to research on detector materials with the objective of developing new and better detectors for solid state dosimetry.

5.1. Stopping Power and Phase Effects

A detailed investigation on stopping powers for electrons and positrons in many tissues and tissue substitutes has been published (ICRU, Bethesda, 312). This report is not just a review of existing stopping power data but includes new calculations based on a detailed analysis of experiments and electron stopping power theory. Thus it was possible to eliminate some systematic

errors in earlier tabulations and the new tables may represent the standard electron and positron stopping powers for the next decade. In consequence of this improved data, also some inconsistencies in electron W-values have been explained and removed.

Stopping powers and penetration depth of electrons and heavy particles were investigated experimentally (Univ. Dundee and St. Andrews, 463) with particular regard to chemical binding and physical phase effects. Chemical binding effects depend on the nature of the chemical bond and were observed to range up to 15% for triple bonds. For information on the physical phase effects, the ionization potential of some polar liquids, possibly the most important parameter in stopping power calculations was investigated (CPA, Toulouse, 295). In this work, the onset of ionization was measured with photons of 6 to 10 eV using the capture of electrons in liquid water by nitrousoxide as a scavenger. Although precise values have not yet been obtained, it was observed that the ionization potential of water in the gas phase is at least 3 eV greater than in the liquid phase.

Chemical bonds and the structure of molecules are also important for pion-dosimetry. Due to the evidence that atomic capture probabilities of pi-mesons are dependent on molecular structure, not only the elemental but also the molecular composition of materials must be considered (Univ., Surrey, 526). Therefore the problem of tissue substitutes for pion dosimetry was investigated and five tissue equivalent and two bone equivalent mixtures calculated for this purpose.

5.2 KERMA Factors and Neutron Transport

KERMA, i.e. the kinetic energy released in material, is an important piece of dosimetric data for neutron dosimetry. A new method of evaluating fluence-to-KERMA conversion factors with low-pressure proportional counters was developed and applied (Univ., Homburg, 298; PTB, Braunschweig, 284). KERMA factors were evaluated for fast neutrons between 13.9 and 19 MeV for some wall materials (A-150, C, Mg, Al) commonly used in neutron dosimetry. The measured KERMA factor of A-150, a plastic employed for its equivalence to soft tissue, at 19 MeV is significantly lower than the value calculated from basic nuclear data, indicating an unacceptable uncertainty still existing at high neutron energies. Measurements with a graphite proportional counter also provide strong evidence that the neutron interaction with carbon giving rise to 3 alpha particles occurs, in the energy range between 17 and 19 MeV, at significantly lower probability than reflected by the values used in the cross-section libraries, and possibly accounts for some of the uncertainties regarding KERMA factors for high energy neutrons in tissue and tissue like materials.

Neutron radiation transport calculations, using cross-section data libraries as input data, were performed as part of the development and application of transport calculation codes for particular purposes (CENDOS, 311; EURADOS, 507; KFA, Jülich.

288). The results obtained are described in this synthesis within the relevant context. Within the present section of data and methods it is, however, useful to elaborate somewhat on the improvement in theoretical methods.

Several numerical methods for deriving organ and tissue doses were applied and intercompared (CENDOS, 311). In general, the results in the ICRU sphere agree well with the unified set of conversion factors evaluated and recommended recently on a Workshop "Radiation Protection Quantities for External Exposure", organized by the Commission and the PTB, Braunschweig with the co-sponsorship of the International Commission on Radiation Units and Measurements, ICRU (see Annex V).
Benchmark calculations were performed with different codes on neutron spectra from light and heavy water moderated californium sources (EURADOS, 507). This test is not yet complete due to difficulties experienced in the dissemination of input data.

Finally, neutron transport and energy deposition codes were combined to a code for microdosimetric investigations in which radiation transport, e.g. in detector walls, can not be neglected (KFA, Jülich, 288). This new code was applied to the development of tissue equivalent proportional counters for the measurement of dose equivalent.

5.3. Concepts, Methods, and Data of Microdosimetry

A detailed report on the concepts, principles, methods, data and applications of microdosimetry has been published (ICRU, Bethesda, 312). This report is the first comprehensive documentation on microdosimetry and has become an important source of information on this field.

Calculations of d(y), i.e., dose distributions in terms of lineal energy y, were performed by several institutes. They were calculated for several mixed neutron-gamma fields in support of the development of a microdosimetric counter for dose equivalent (KFA, Jülich, 288). Distributions d(y) were further calculated for low neutron energies (1 to 100 keV) for which there has been little or no data available until now (Univ., Dundee and St. Andrews, 463). In a joint project, d(y) for very small simulated diameters, below 0.3 μm was evaluated (IFNL, Legnaro, 297; GSF, Neuherberg, 287). It is interesting to note that at such small diameters the distribution depends just on charged particle straggling because the site size is too small to significantly slow down the recoil particles within the site.

In one of the institutes (GSF, Neuherberg), the effect of straggling was in fact studied in detail (CENDOS, 311). Preliminary results have been obtained and this activity is being continued, in collaboration with the National Bureau of Standards, NBS, Washington. Further, a new library of secondary charged particle spectra was set up again in collaboration with NBS. This collaboration also evaluated differential and integral ion yields of protons, deuterons, alphas and heavy ions, allowing

for the consideration of specific ionization along particle tracks. This is of considerable importance for the computation of microdosimetric quantities and for investigating the difference between energy-deposition and ionization distributions. For this type of application, preliminary results were obtained.

5.4. Concepts and Data for Dosimetry of Incorporated Radionuclides

Investigations on beta emitting radionuclides, aiming for practical application to radiation protection in future, are at present still at a fundamental level.

The lyoluminescence of organic and inorganic phosphors with radionuclides (H-3, C-14, F-18, S-35, I-125) incorporated into the matrix of these phosphors was investigated in a study of the feasibility of dosimetry of incorporated soft beta emitters (Univ., Aberdeen, 310). The sensitivity of the measurement of radiation dose from incorporated emitters is essentially the same as in the case of external irradiation. For mannose the smallest detectable dose is about 50 mGy without the use of sensitizers. For bromouridine and iodo-deoxy-uridine (without sensitizers) it is in the order of 10 and 25 Gy respectively. It was also shown that there exists a linear relationship between the concentration of free radicals, as measured by electron spin resonance and the lyoluminescence signal.

The microdosimetry of incorporated radionuclides was investigated with the aim of developing a new concept of internal dosimetry taking into consideration the very high local energy density at the site of disintegration of some radionuclides (KFA, Jülich, 288). In the review period, the soft electron emitters (I-125, I-123, Cu-64, Fe-55 and H-3) were taken as examples, and the necessary framework of concepts, codes and physical data was developed in terms of number and energy distributions, energy potentials of multiple vacancies, and energy imparted. When evaluating the energy imparted to small sites around a decaying atom, calculations were performed for condensed phase and an isolated atom (gas phase). A difference arises due to the multiple ionization potential remaining on the isolated atom after the disintegration and being locally absorbed in condensed phase. This energy potential is 1.1 keV for I-125.

5.5. Charged Particle Tracks

Investigations of charged particle track structure were performed both theoretically (GSF, Neuherberg, 563 and 287; MRC, Harwell, 412; Univ., Würzburg, 286) and experimentally (AERE, Harwell, 306; Univ., Strassbourg, 294).

Monte Carlo track-structure calculations were applied to the evaluation of microdosimetric distributions of tritium in water vapor (GSF, Neuherberg, 563) as an attempt to better understand the expression of biological effectiveness of this radionuclide. Calculations were performed for homogeneously distributed tritium sources and site sizes of 0.1 to 1000 nm, but also for tritium

specifically incorporated in the target. For the smallest sites, the excitation potentials of water vapor strongly influence the distributions of energy imparted. Similar calculations were performed for I-125, but are not yet fully evaluated. In another project (GSF, Neuherberg, 287) considerable efforts were made to simulate electron and proton event tracks in water vapor and to analyze their morphology in order to provide a better description of radiation quality. For this latter purpose, a new method of stochastic sampling of transfer energies in spherical targets was developed. Other tools, such as neighbour-distance analysis, amalgamation of event agglomerates and cluster analysis were applied to describe track morphology.

Track structure codes were applied for calculating energy deposition of ultra soft X-rays, protons and alpha particles to cylindrical targets of 1 - 100 nm including dimensions of DNA structures (MRC, Harwell, 412, in collaboration with GSF, Neuherberg, and Columbia University, New York). A consistent set of distributions of energy imparted has been generated. Preliminary comparison with observed RBE of alpha particles of different energies imply that energy deposition of 300 eV (or greater) in a nucleosome-sized target may be a biologically critical property of high-LET radiations. Further, the probability of energy deposition of 100 eV (or greater) from ultra soft and hard X-rays in spheres of 3 nm diameter correlate well with RBE's observed for these low LET radiations.

A new algorithm for the computer simulation of charged particle tracks has been developed (Univ., Würzburg, 286) which is largely analogous to and compatible with that of Columbia University, New York. Apart from the computations of stochastic functions (proximity functions and geometric reduction factors for electrons and neutron recoil ions) there has been an extensive study in terms of average values; this has concerned the build up process of secondary electrons for the high energy heavy ion beam at the BEVELAC accelerator. The result of this work has been a substantial relaxation of the dimensions of chambers in which microdosimetric studies at BEVELAC need to be performed.

Charged particles tracks, observed experimentally with a cloud chamber, were obtained for low energy electrons, 85 - 390 keV protons, and 1.1 - 5.3 MeV alpha particles (UKAEA, Harwell, 306). Tracks were observed and photographed in a new tissue-equivalent gas mixture and in water vapor. Provisional W-values and stopping powers have been derived as well as y distributions and interdroplet distances. Results with the new tissue-equivalent gas mixture were scaled to water vapor and compared with earlier work in a different gas mixture and also with track structure calculations (GSF, Neuherberg, 563). Agreement was found to be within 10% which increases confidence in the cloud chamber analysis and in the track-structure calculations.

Experimental work on charged particle tracks has also been performed in the condensed matter (Univ., Strasbourg, 294). The microscopic analysis of alpha tracks crossing ionographic media

led to the discovery of thick protuberances which, on the basis of systematic experiments, are called strong ionizing events and are identified with short tracks of recoil ions ejected by elastic scattering. The number of strong ionizing events increases with the primary's energy and their production is more than an order of magnitude larger than that of Rutherford recoils. A more recent objective in these studies is the investigation of gap distributions along alpha particle trajectories. A semi-automatic measurement assembly has been developed to process such gap distribution. This experimental work on alpha-particle tracks in condensed media is supported theoretically by calculations of double differential cross sections. Improved agreement with experimental differential cross sections of molecules is obtained by a mixed treatment combining different quantum mechanical approaches for the deeper and higher atomic shells.

5.6. Research on Detector Materials for TLD

Research on luminescent materials has been performed with the aim of improving solid state dosimetry (NRPB, Chilton, 309; AERE, Harwell, 459; CENDOS, 311).

Work on the implementation of thermoluminescence techniques to dose measurement under operational conditions (NRPB, Chilton, 309; UKAEA, Harwell, 459) has involved the investigation of the electron phototransfer process in lithium fluoride and its practical application to the re-assessment of absorbed dose, the investigation of the characteristics, and practical dosimetric applications of thermoluminescent materials. In particular materials which offer the combination of high sensitivity and tissue equivalence have been studied. Finally studies in the photon energy response have been performed as well as the properties of energy discriminating shields for use with high sensitivity materials for application to the measurement of environmental radiation. Further the measurement of dose with chips (TLD-700) at temperatures up to 130°C and the use of U.V. in sensitization has been investigated (UKAEA, Harwell, 459). Glow curves have been recorded for analysis with a view to obtaining a coherent picture of the effect.

The response of thermoluminescent materials to neutrons has been studied (CENDOS, 311) using glow-curve analysis in multipeaked thermoluminiescent dosimeters. The difference in LET dependence of two main glow peaks of TLD-300 has been used for the measurement of fast neutron and gamma-ray absorbed dose. Finally a review has been prepared on the neutron response of a variety of thermoluminescent materials. The efficiency ratio was shown to be essentially constant for a given thermoluminescent material for neutron energies from thermal to about 10 MeV.

6. PERSPECTIVES AND RECOMMENDATIONS

In individual neutron dosimetry no fully appropriate detector is as yet available. Despite of many efforts and promising progress, there is still a sensitivity gap between 20 and several hundred keV with individual dosimeters used in radiation protection practice. Further individual dosimeters in general have a protective layer much thicker than 70 μm and thus do not conform with the European Directives for beta and low-energy X-rays. These problems of the individual dosimetry of neutrons and of low energy beta and photon radiations require further study and development.

Shortcomings of the conceptual basis for individual dosimetry appear not to have been completely resolved by the recent ICRU specifications of new operational quantities for dose equivalent. It is clear that further effort is required within the Community to coordinate the approaches to this problem within the Member States.

There is still uncertainty concerning the quality factor, one of the most important ingredients in the numerical definition of the dose equivalent quantities. The recent discussion of the ICRP to double the quality factors for neutrons is merely an interim step towards a definite revision of the quality factors. The Commission's Radiation Protection Programme will be an important source of information for any such revision.

The results on RBE of densely ionizing radiation are far from definite. Improvement is needed particularly with regard to the following problems: - few studies have yet reached doses that are sufficiently low to be directly relevant to radiation protection, - often there is a lack of numerical estimates of uncertainty, - even the mathematical methods to achieve such estimates are still incomplete, apart from the actual biological or epidemiological uncertainties. In addition, biophysical modeling in respect to RBE of densely ionizing radiations has led to the appearance of further complexity in the biological response. Progress in understanding the limitations and similarities of biophysical models must be sought if appropriate decisions with regard to the revision of quality factors can be made. There is a need to identify the real differences and equivalences of seemingly divergent models. These must be supported by biological experiments in order to understand radiation carcinogenesis.

When considering the activity of the Radiation Protection Programme 1980-1984 in the field of charged particle tracks, one notices a considerable shift in comparison to the foregoing programmes. In the seventies the European Community was leading in microdosimetry research with regard to track-structure calculations; both the conceptual framework and the first computer codes were in fact developed within the Commission's earlier Radiation Protection Programmes. But in the programme 1980-1984 there were no studies of the spatial and temporal

development of radiation species, a method developed by US-scientists in the late seventies. Although it must be acknowledged that the European laboratories during 1980-1984 concentrated their efforts on the application of microdosimetry to both practical radiation protection and elucidation of low dose effects, the apparent lack of fundamental microdosimetry research is a matter of concern with regard to future conceptual and technical innovations.

The interpretation of epidemiological data with microdosimetry has partly been delayed by difficulties in getting access to existing Japanese data bases. Easier access to data bases should be one of the problems to be considered within the Commission's collaboration with overseas national organizations.

There is an increased confidence in the ability of computational methods to predict three-dimensional dose distributions in complex objects such as the human body. A possible consequence is that computational methods may now be used to provide conversion factors from radiation field quantities such as air kerma and neutron fluence to both primary and secondary dose quantities rather than resorting to the direct implementation of the latter quantitites in the form of physical standards. This development requires more precise interaction cross-section libraries. The knowledge of cross sections and energy transfer coefficients in condensed media used in track structure calculations is still based on radiation interaction with gases and even these data are uncertain within a factor of 2.

SECTOR B

BEHAVIOUR AND CONTROL OF RADIONUCLIDES IN THE ENVIRONMENT

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4. Perspectives and recommendations

1. PURPOSE AND GENERAL VIEW

The Programme of the Sector "Behaviour and Control of Radionuclides in the Environment" is directed to the acquisition and improvement of data on the behaviour of all the radionuclides (natural, man-made) released in various ecosystems in different circumstances and within the framework of the different applications of nuclear energy.

During the transfer to man radionuclides may be retarded by interactions within ecosystems ; they may change in concentration but also in quality (chemical speciation of the radionuclides) with time. On the other hand, the long-lived radionuclides may enter in a cycle (biogeochemical cycle) and be stored in different compartments of which the bioavailability characteristics may be very different. These modifications may imply a variation in time of the parameters which condition the exposure level of living organisms. Current radioecological assessments rely heavily on the use of ad hoc models to estimate the dose to man. These models utilize a number of input parameters leading to a sometimes very large uncertainty of the doses assessments.

In the case of unplanned releases, the estimation of time-dependent exposure rates from the radionuclides requires dynamic models. Again an extensive data collection is needed for these quite flexible models, which have however a great complexity not always leading to an enhanced accuracy.

Validation of these time-dependent predictions can be corroborated by long-term experiments with radionuclides or by using substituting chemical analogs which may give a good picture of the long-term behaviour of the radionuclides.

2. RADIONUCLIDES TRANSFER IN ECOSYSTEMS

2.1. Marine water environment

2.1.1. Purposes

In the case of the majority of artificial radionuclides likely to be routinely introduced to the marine environment during controlled waste disposal operations knowledge is now available to ensure that such introductions can be effected without undue radiological hazard. However a detailed understanding of the mechanisms leading to the observed distributions, and consequent radiation exposures must be further developed. This is especially true when the significance of the longer lived radionuclides for human radiation exposure over long periods of time (millennia) is considered. It is also true in relation to particular segments of the marine environment and perhaps especially so in relation to the deep-sea with its cost-effective use as a disposal environment. There are a number of significant events which have occurred lately that ask for important changes

in the priorities of Community radiation protection research. One which might be singled out is the increasingly important need to assess the consequences of a spread of radionuclides over wider oceanographic areas in the calculation of collective dose and collective dose commitment and longer spans of time. Collective dose evaluations are particularly useful for the comparison of practices and optimization under similar conditions notwithstanding the uncertainty (sometimes rather large) affecting their absolute values.

It should also be recognized that many of the data collected on the already existing radioactivity in the environment may contribute to an improvement of the understanding of the basic of the mechanisms of marine ecology and oceanography. This is particularly true for areas like circulation and mixing of water masses, chemistry and physico-chemistry of seawater and sediments, metabolism of marine organisms, marine ecology, and marine instrumentation. Radiation protection research has also produced much information concerning the behaviour of non-nuclear marine pollutants.

2.1.2. Behaviour of radionuclides in coastal waters

In sea water, the chemical speciation of Np and Pu away from the immediate discharge areas appeared to be primarily Np(V) and Pu(V), whereas, Am is present in more than one chemical form. In sediments a considerable amount of mixing is occuring by bioturbation, the long-term consequences of such bioturbatory effects are being incorporated into a mathematical model to describe the role of sediment/nuclide interactions in shallow sea areas (MAFF, Lowestoft, 331).

A large number of sorption distribution coefficient (Kd) values for Eu-152, Ce-144 and Am-241, have been found to vary considerably between 0.4 and 2×10^5. Apparently using Eu as a homologue for Am is rather a sound idea when predictions on the long term behaviour of Am are to be made. The transfer of Am and Pu to benthic species is weak. Some species absorb Am-241 from both interstitial water and directly from sediments. Others absorb only from the water phase (CEA Cadarache, Cherbourg, 316),

The function of the seaweed Fucus vesiculosus and the mussel Mytilus edulis as bioindicators in waters of different temperature and salinity regimes has been studied. For nearly all elements assessed such as Pu, Am, Cm, Np, Eu, Ce, I, Cs, Zn, Co, Fe, Mn and Cr, Fucus has the highest transfer factor. For lanthanides and perhaps also actinides, the whole set of experimental data however suggest that Mytilus might be a more stable bioindicator than Fucus, where the content is a balance between very rapid accumulation and losses. The contamination of the benthic fauna with Pu and Am has been estimated at Thule, Greenland, from models describing the distribution of the contamination. Benthic bivalves concentrate Am relative to Pu from the sediments. Sampling cruises in the North Atlantic and the Arctic Area have permitted the distances of the spread of

radionuclides discharged in more southern parts of Western-Europe to be screened. Radiotracers like Cs-134 and Tc-99 are found at 7000 km from their discharge points after 7 years, diluted by a factor 10 when entering the Arctic Ocean compared to the North Sea and by a factor 300-500 when entering the East Greenland current. Pu-239,240 is not spread in the same way through the oceans (RISØ Nat. Lab., Roskilde, 339).

It has been shown that enhanced discharges of Tc-99 already started from reprocessing in Western Europe in 1970. Experimental studies have confirmed that pertechnetate is stable in sea water within a large interval of pH and redox potential since normally marine sediments do not accumulate technetium to any appreciable extent. However, fine grained sediments, rich in organic carbon may rapidly and almost irreversibly immobilize Tc. Compared to phytoplankton macrophytic brown algae accumulate more Tc (ENEA, S. Teresa, 322). Chromatographic analysis of Tc, accumulated in algae and a Flavobacterium showed the reduction of TcO_4^- and complexation with various organic compounds (IRSNB, Brussels, 485). A box model of the distribution of Tc developed at ENEA (Forte S. Teresa, 322) indicated that marine food chains are probably not an important pathway for the transfer of technetium from the environment to man.

In the Gulf of Gaeta, fed by water from the river Garigliano on the banks of which a reactor was operated from 1966 to 1978, the concentrations of Cs-137 in both the biotic and abiotic matrices were not different from those found in other coastal environments. The power plant contribution therefore does not exceed the fallout contribution, except for Co-60 (ENEA, Forte S. Teresa, 322).

Measurements of Cs-137 and Cs-134 in fish caught in the Irish Sea seem to show that the radiological impact of the Sellafield discharges for the exposed population presents little cause for concern. No beta radiation in excess of Cs-137 was found which would have originated from the Sellafield plant (Dept. Pure Appl. Physics, Univ, Dublin, 338).

An International Symposium on the Behaviour of Long-lived Radionuclides in the Marine Environment was held at La Spezia, Italy (28-30 September 1983) (see annex V). The very low contribution to the effective radioactive dose delivered to the marine environments by the discharges from nuclear power plants was emphasized during this seminar. The low radioecological sensitivity of the marine environment will have to be considered when we will decide upon the future final disposal of radioactive waste. It is thus vitally important for the reliability of any environmental model that it should be based on more accurate observations in the field or at least in the laboratory.

2.1.3. Behaviour of radionuclides in estuaries

In the Esk and adjacent region, work on the ecological aspects of alpha emitting radionuclides (NERC, The Hoe, 438) brought to light the hitherto unknown presence of hot particles consisting predominantly of U, Np, Pu, Am and Cm radionuclides in sediments washed by effluents from the reprocessing of nuclear fuel. In terms of mass these hot particles often consists predominantly of uranium (depleted U-235), Np, Pu, Am and Cm radionuclides (plus various gamma emitters). Hot particles were especially abundant during peak releases of radionuclides in the mid 1970's. Plutonium isotopes from the North Sea, where Pu-238/Pu-239+240 isotopic ratios are high due to the releases from reprocessing plants, are found in the Dutch delta area. A listing of the gamma emitter content of sediments and various plant species has been set up (DIHR, Yerseke, 326).

When freshwater meets seawater a major augmentation of salinity of the freshwater occurs but also a minor decrease of charge takes place resulting in a reduction of Kd values of different radionuclides such as Fe-59, Mo-99, Tc-99, Cr-51, Cs-137, Mn-54, Zn-65, Na-22, Co-60 (CEA, Cadarache, 317).

In brackish water, the effect of ageing on the distribution of Am in different chemical forms showed an increasing fraction of particulate associations containing Am(III), a decreasing fraction of dissolved Am and a strongly increasing part of adsorbed Am(III). In the brackish media containing Am(III) and humic acid, an Am-humic complex was detected by chromatographic analysis. The uptake of Am(III) by a test organisms is reduced by EDTA (BAH, Hamburg, 559).

Problems of the Behaviour of Radionuclides in Estuaries have been discussed thoroughly at a Seminar held at Renesse, September 1984 (see annex V). Some serious questions remain with relation to the significance and the general applicability of sequential extraction techniques, particularly in regard to their relevance for solid phase speciation ; nearly all parameters are available to describe the equilibrium condition in a contaminated ecosystem, however in the case of accidents more information on the dynamic processes which can occur in an estuary are needed.

2.1.4. Behaviour of radionuclides in deep sea water

The objectives of the studies have been to learn more about the basic radioecology of the deep sea environment (MAFF, Lowestoft, 331 and NIOZ, Den Burg, 509). At NIOZ the composition, density, biomass and vertical distribution of benthic micro- as well as macrofauna has been very systematically described. At MAFF the sedimentation rates and depth and rate of bioturbation have been modelled using C-14 and Pb-210 data. The incorporation of Pb-210 to depths in sediment of about 8 cm provides clear evidence that mixing by biological processes occurs. C-14 profiles corroborates this finding. Laboratory experiments made clear that Pu(IV) is adsorbed and desorbed more readily on sediments

with a high carbonate content. Models appropriate to the estimation of dose-rates to the deep sea fauna are being developed.

2.1.5. Remobilisation of radionuclides and subsequent transfers

Two institutes have done comparable experiments on the transfer of radionuclides from the seawater surface to atmospheric aerosols (CEA, Cadarache, 466 and AERE, Harwell, 333). The equipment used by both institutes collected fine aerosol droplets produced by a system bubbling underneath the seawater surface layer. They find a real enrichment of some elements in the aerosols. The enrichment factors found in the AERE experiment ranged between 29 and 419 for the sum of Pu-238, Pu-239+240 and Am-241. This enrichment exceeded a factor of 2000 in the CEA experiment. Both laboratories agree on the fact that this enrichment is due to the presence of particulate matter in the aerosols, on which the Pu and Am is absorbed. Cs-137 and activated corrosion products are much less enriched in the aerosols.

The results of the study on remobilization of actinides from estuarine contaminated intertidal sediments have shown that they are not permanent sinks for actinides deposited with sediments, but merely temporary depositories which can become net sources when the input of actinides is significantly reduced. There is evidence of a loss from this ecosystem via suspended sediment. This may be either the result of leaching of plutonium from sediments by fresh or brackish water, resorption by suspended material as the salinity increases and eventual transport from the estuary on the ebb tide, or the result of the physical resuspension of the sediment deposits by current and wave action under certain conditions (UKAEA, Harwell, 334).

2.1.6. Cellular biochemistry of radionuclides in marine organisms

The uptake of U, Pu, Am and Cm in Mytilus edulis, the common mussel is believed to occur predominantly by direct uptake of dissolved species from seawater and not from food. The proportion of uranium in the mussel which is derived from BNFL debris is insignificant relative to that from natural sources. Investigating the subcellular distribution, it was shown that the alpha activity of cell cytosol is associated with discrete molecular weight fractions. Retention in tissues is mainly associated with proteins and the biological half-lives of the transuranics are similar to those expected for proteins (i.e. 1 year gross) and not similar to those expected with passage of sediment throughout the digestive system (NERC, The Hoe, 438). In cockles and winkles, americium is found in lysosome fractions of the cells bound to proteins of high molecular mass. Murex accumulates Am(III) very rapidly where it was shown that after 3 days of contamination Am is incorporated in the hepatopancreas cells, mainly associated with the lysosome-mitochondrial subcellular fraction mainly. This trend is also perceptible in

star-fish. In E. Coli, Am(III) is almost exclusively bound to the cell membrane (Lab. Biochimie, Univ. Nantes, 435).

Technetium accumulates predominantly in the pylorus of starfish independent of its chemical form. A gel filtration of the cytosolic compounds of these pyloric cells revealed the chelation of Tc with heavy compounds of about 150.000 gram/mole and with light compounds of 10.000 gram/mole, the latter being within the molecular mass range of metallothioneins.

2.2. Fresh-water environment

2.2.1. Purposes

The nuclear industry, besides releasing low level radioactive material into the environment, particularly into water, releases also non-radioactive chemicals and heat. The possible interaction of these three factors should be given due consideration especially in fresh-water ecosystems. Surface-water bodies are much more variable in composition and physical characteristics than the marine environment. This necessitates studying the local conditions in which transfer of radiocontaminants will possibly occur (e.g. transition from surface-water to marine ecosystem). Biotic and abiotic factors may influence the radionuclides transfer process and consequently the radioecological evaluations.

2.2.2. Behaviour of natural and artificial radionuclides

The sediment of the river constitutes the principal compartment retaining the U and Ra which may be released from the uranium mining and processing site of Lodève. In the water phase Ra^{2+} and complexed U are the important forms of both radionuclides. When used as irrigation water, transfer of Ra to some agro-alimentary products may occur with a transfer factor ranging between 6.9×10^{-4} and 9.2×10^{-5} (Bq/kg fresh weight/Bq/kg dry soils). Actually, the effects of the exploitation of the mine are perceptible at very small distances only (CEA, Cadarache, 321, 528).

The Am-241 speciation in water can only be explained by integrating the effects of a complex set of competitive interactions such as e.g. hydrolysis, pseudocolloid formation and complexation reactions with inorganic anions (HCO_3^-) or with humic acids. The water type may also have a pronounced effect on the bioaccumulation of Am-241. The claim that microbial activity could profoundly change the behaviour of Am-241 in sediments and water was not proven (SCK/CEN, Mol, 329). Bioaccumulation studies of Am-241 indicated the two major processes that are responsible for its accumulation in freshwater animals. The first which accounts for more than 80 % in crayfish, occurs by external fixation on the carapace, while the second appears to come about by oral uptake, followed by a true assimilation within the organs. In crayfish organic compounds like cellulose derivates may increase the Am-241 availability by a factor of

about 5. Lymnea, a pond snail, quickly accumulates Pu-237 and Am-242 from water in hepatopancreas tissues with plasma membranes, mitochondria and lysosomes. The transfer factors are inversely correlated with the specific conductivity of the water.

Tritium applied as HTO is rapidly taken up and released by the unicellular algae Acetabularia acetabulum and Boergesenia forbesi as well as by the pluricellular algae Cystoseira compressa and Laurencia obtusia. Tritium becomes incorporated into the total organic matter of the algae mainly through the photosynthetic process, (CEN/SCK, Mol, 431). After contamination of Scenedesmus quadricanda with HTO, leucine and arginine of the amino acids turned out to contain the highest activity levels. In lipids the highest tritium content was found with monovalent unsaturated fatty acids of C 16:1 and C 18:1 structure. The intestinal absorption of glutamic acid, retained by absorption sites such as intestine, liver, gills, kidneys, blood and muscles, depended on its concentration, following a saturation kinetics (Inst. Strahlenhygiene, BGA, Neuherberg, 313).

Concentrations of 3.7×10^7 Bq/ml culture medium reduced cap formation in Acetabularia and provoked some morphological anomalies. At the same concentrations, tritium had no effect on the growth rate of Chlamydomonas and Dunaliella (CEN/SCK, Mol, 431).

The study of the impact of waste from PWR nuclear power stations on the Meuse ecosystem made by a multidisciplinary team aimed primarily at studying thoroughly the basic mechanisms governing the concerned environment. The estimation of the impact of these thermal and chemical releases from the nuclear power plant must be considered in the general ecological context of the industrial and urban pollution of the region under consideration. The impact of the radioactive releases has noticeably decreased and the releases from the nuclear power plant at Tihange have only little effect on the invertebrates and the fish used as radiocontamination tracers. Microscopic algae show to rapidly concentrate various radionuclides. The hypothesis of tritium fixation on organic molecules within the reactor of the PWR power plants, has been quantitatively estimated (CEN/SCK, Mol, 330). The latter may have some importance for explaining the difference in specific activity between living forms and water.

2.3. Terrestrial environment

2.3.1. Purposes

The early data on amounts of radionuclides accumulated in crops and soils were derived from studies following fallout from weapons testing. Isotopes of strontium, caesium and iodine and plutonium were of primary interest because they contributed most to the radiation dose received by man. These investigations have however several limitations since transfer pathways such as root uptake, resuspension, interception of airborne radionuclides by foliage were considered for a narrow range of crops only, mainly

grass and cereals. The emphasis was mainly placed on regional rather than on local dose assessments, data for soils from one location being combined with data for plants from another location. A difficulty inherent with these experiments was the need to use toxic levels of the radionuclides due to the insensitivity of the detection methods. This inevitably affected uptake.

Additionally the experimentally determined transfer factor may be inappropriate simply because essential information describing the experimental conditions such as climate, fertilizer application, time of radionuclides application, chemical form, depth of contaminated soil layer and time of harvest, were not recorded . During the last decade many computer models have been developed to predict doses to man resulting from radioactive releases (either routine or accidental) making the shortage of relevant data on soil-to-plant transfer factors under realistic field conditions all the more obvious.

The development of nuclear power programmes has moreover directed the attention towards many additional radionuclides which may potentially be released into the environment, such as Mn-54, Co-60, Zn-65, Ru-106, Sb-124, Cs-137, Ce-144, Th-229, Np, Pu, Am and Cm as well as the fission products Tc-99 and I-129.

2.3.2. Behaviour of radionuclides released in routine conditions into the soil-plant ecosystem

The contribution of nuclear weapons fallout to the Pu-239+240 and Am-241 in arable soils and crops was measured in soils from SW England where the highest concentration of actinides are found. The Am-241 soil to plant transfer factors in grass and barley grain were 2 to 5 time bigger compared to those of Pu-239-240 (AERE, Harwell, 333). Yet, studies of the mean values of transfer factors of the same radionuclides on different European pastures showed no differences (RIVM-ITAL, Wageningen, 325). In both studies the concentration factors were about 10^{-2} on a dry weight basis. Transfer factors of Pu and Am measured in potato peel and flesh were very comparable to each other. They were however at least a factor 10 lower in potato peel than those found in pasture grass (NRPB, Chilton, 336). A residence time model for Pu migration in soil has been derived based on a long-term collection of data. The spread of the data however is large, which must mainly be ascribed to a 25 year sampling period of normally grazed pastures. The migration rate of Pu and Am remains very low, with indications that this may be due to colloid formation (RIVM-ITAL, Wageningen, 325). The behaviour of fallout plutonium in some soils in Italy showed that human activities prevailed over the different soil characteristics in determining the surface distributions of Pu-239,240 and Pu-238 (ENEA, Casaccia, 323). In the UK, the disposition of Am-241 is dominated by the oxide and organic phases. Less than 4 % of the applied activity remained readily available after 6 months. In peat more than 80 % of the activity was found with the organic phase (NRPB, Chilton, 546). The migration of Pu-239+240 and

Am-241 was slower in coniferous than in deciduous woodland or grassland. The highest concentrations were found at 2 to 4 cm depth humus layer of the coniferous ecosystem (AERE, Harwell, 333).

The observed levels of Pb-210 and Po-210 in a cattle pasture varied from 6 to 88 Bq/kg and 9 to 15 Bq/kg, respectively, throughout the year, those in the sheep pasture from 7.4 to 53 Bq/kg and 5.4 to 23 Bq/kg respectively (NRPB, Chilton, 545). With Pb-210 air-plant transfer exceeds the soil-plant transfer (TH, Darmstadt, 487).

The importance of vegetation of an ungrazed salt-marsh in the trapping of radioactive material bordering the Ravenglass estuary was proven with levels in the vegetated areas being three times those on open mud (NER, Cumbria, 439).

Lignites burned in Coal Power Plants (CPP) contain natural radioactive nuclides, especially in the uranium series. Measurements of these radionuclides were done at two places in Greece, Kardia and Ptolemais. The results show that Ra-226 concentration is higher in soils collected along the line in the main direction of the prevalent local wind, due to the deposited fly ash (Nucl. Phys. Dept., Thessaloniki, 533).

Models for long-term tritium behaviour have usually been based on the assumption that equilibrium is attained between all compartments of the biosphere. This however is not valid near sites of releases and particularly not after accidental releases. Moreover, tritiated compounds entering the biosphere may also be converted into a great variety of compounds (organic bound tritium = OBT) with widely differing transport and metabolic characteristics.

Predictions of the tritium contamination of the soil can be made with the help of a field-tested condensation formula and a tritium transfer model on the basis of site-specific meteorological data and tritium release rates. During the diffusion of moisture through the soil there is an accumulation of HTO due to isotopic effects, which almost doubles the specific activity of the gain in the rooting zone of plants compared to the atmospheric label (GSF, NIR, Hannover, 314). A dynamic model has been developed idealizing the soil-plant-atmosphere tritium transfer. The numeric solution of two linear differential equations corresponds, respectively, with different soil layers, and several plant compartments (CEA, Cadarache, 340). The research on the transfer of tritium oxide after either a unique deposition or routine releases shows the incorporation of a definite fraction in the organic matter of the plant, varying in the different plant systems (CEN-SCK, Mol, 431). Binding of non-exchangeable tritium in plants occurred by photosynthesis. Experiments on the incorporation of tritium showed 20 % of the organic bound H being readily exchangeable with tritiated water (CEA, Cadarache, 340). A European Seminar on the Risks from Tritium Exposure was held at Mol, jointly organized by the CEC

and CEN/SCK Mol (1982) (see annex V). A coordinated working group on tritium met several times in order to discuss progress and to orientate research.

The data of the work on the uptake of C-14 by various crops from residual organic matter decaying in soil show that the highest concentration of C-14 is present in roots, followed by leaves and stems. For roots, the activity represents probably adsorption and contamination with soil. The total annual transport from soil to plant of C-14 for each crop (taking into account only aerial parts) was always less than 1 % of the original C-14 activity present in the soil (CEN/SCK, Mol, 431).

Lysimeter experiments (RIVM-ITAL, Wageningen, 325) showed a decreasing order of transfer factors for Zn-65 > Sr-90 > Mn-54 > Cs-137 > Co-60. When the geometric means of these transfer factors studied with different plants and on different soils were calculated, they were found to be fairly close to those described in the Report NUREG/CR-2975, UCID-19463, 1982. These geometric means however cover a large spread of data. For this reason, a "working group" collecting data from European research institutes was set up by the International Union of Radioecologists (IUR, Oupeye, 468) in order to come to a statistical description of the soil-plant transfer relations of radionuclides. Moreover, in order to encourage the exchange of information and cooperation in the fields of radioecology, IUR has sponsored a number of workshops, meetings and other related activities (see annex V). A lysimeter set up at KFA (Jülich, 560) and used to study the Co-60 and Cs-137 under different conditions showed indeed the variability of their transfer factors. The residence time of the radionuclides in the soil must also play a role in their behaviour, Cs-134 remaining available for only 5 % in clay and 40 % in peat after six months contact, whereas 85 % and 70 % of Sr-85 was still available in clay and peat respectively (NRPB, Chilton, 546).

A comprehensive model developed at UCL (Louvain-la-Neuve, 328) on the fate of technetium in a catchment under forest describes that this would minimally comprise a flow through the upper soil layers towards a stream and the mixing undergone in the stream. Transfer factors of technetium are lower in soils than in nutrient solutions, when the usual expression of Bq/gram soil is used for the soil transfer factor (UCL, Louvain-la-Neuve, 328). When however Bq/ml of soil solution is used no difference exists (RIVM-ITAL, Wageningen, 325). A chemical reduction of TcO_4^- in the presence of complexing agents results in the formation of organic complexes. The reduction can also be brought about by action of soil microbes. The complexes formed have quite low exchange rates (KUL, Leuven, 531). Most evidence points towards TcO_4^- as the most readily available chemical form of Tc for plants with an almost linear proportionality between the contamination level of TcO_4^- and its transfer (CEA, Cadarache, 315). Chemical reduction of TcO_4^- in soils leads to a serious decrease of the Tc transfer (UCL, Louvain-la-Neuve, 328). A linear relationship was also obtained between illumination and Tc concentration in leaves

resulting in high transfer factors. Light-induced reducing power seems a prerequisite to reduce TcO_4^- in plant cells and to complexe it with organic compounds of various molecular weights. In those cells of Anabaena exhibiting nitrogenase activity, technetium is preferentially accumulated rapidly inhibiting this enzymatic reaction (UCL, Louvain-la-Neuve, 328).

A Seminar, co-organized by the CEC and the DOE, USA, was devoted to the Behaviour of Technetium in the Environment, giving the participants the opportunity to present recent results but also to discuss thoroughly the state of the art in this particular research area. This seminar was held at Cadarache, 23-27 October 1984 (see annex V). The main insight acquired about the behaviour of technetium in the terrestrial environment was that its chemical status can readily be changed by the environment. The influence of these changes on its transfer was emphasized. A coordinated working group on the behaviour of technetium in the environment met several times during the considered period.

The I-125 behaviour in soils seemed to be governed mainly by aluminium oxide and iron oxide, the organic matter content and pH (CEA, Cadarache, 315). A mathematical approach showed that iodide uptake from soil can be expressed by a plant growth model equation, even when the available iodide content in soils is modified by e.g. liming (Royal Vet.Agr.University, Copenhagen, 486). A plain action of microbial life on the fixation of radioiodine was demonstrated by a mathematical analysis of the observations which described the immobilization as a sum of three exponentials with the first phase due to microbiological action (KFK, Karlsruhe, 484).

In the framework of the creation of a European Catalogue of transfer factors, three new mathematical formulations were worked out to describe the tritium behaviour in the biosphere, the dry and wet deposition rate of iodine and the accumulation of radionuclides in soils. In the models, the relative radiological risks incurred by man through his nutrition are also described (CEA, Cadarache, 529).

2.4. Atmospheric environment

2.4.1. Purposes

Atmospheric dispersion processes have been studied extensively and various computational methods have been developed. The quality of the predictions derived from dispersion models depends on an adequate knowledge of the quantity and quality of the releases, the site-specific characteristics and meteorological conditions.

The doses to man following such a release and the subsequent transfer of radioactivity are strongly influenced by the following processes occurring at the earth surface :

- Chemical transformations of released radionuclides occurring in plumes ;
- Depositions which reduce the airborne concentrations and enhance the irradiation intensity coming from the soil surface ;
- Introduction of the material in the food chains.

A more reliable modelling of the radiocontamination by atmospheric pollutants is particularly needed in accidental conditions. In fact, in case of reactor accidents releases to the atmosphere will be in general more important than releases into aquatic environments, the terrestrial ecosystem being one of the most exposed.

2.4.2. Behaviour of radionuclides in accidental conditions

Simulated accidental releases of aerosols of CsI and CsCl showed that the soil deposition is not directly related to atmospheric concentration of the caesium but rather to the molecular weight of the aerosol, the deposition of CsI being greater than the one of CsCl. When the atmospheric concentration increases, the ratio between absorption in the leaves of plants and the deposition on the leaves diminishes, and is smaller for CsI than for CsCl. CsI moreover is more readily washed off the leaves than CsCl (CEA, Cadarache, 530).

The transfer of radioactive materials in the terrestrial environment subsequent to an accidental release to atmosphere was the subject of a seminar held at Dublin, April 1983. The use of simple models and experiments on root-uptake made under real agricultural conditions were stressed. Both good experimental and good theoretical work was needed since no serious progress can be anticipated without close cooperation in the future between both types of scientific approach in view of the complexity and interdisciplinary nature of these matters.

2.4.3. Behaviour under normal releases and natural conditions

Kr-85 accumulates in the atmosphere, its concentration being directly correlated to the world reprocessing activities. The synergistic action of Kr-85 and chemical pollution showed that the increase in aerosol formation may be explained by an enhanced transformation of SO_2 into H_2SO_4, but also by aerosol formation around ions. The calculations show that the transformation of SO_2 by both gamma radiation and UV is a cumulative process at high dose rates (> 1 μGys^{-1}) and a synergistic process at low dose rates (R.U., Gent, 327).

The natural alpha active aerosols in dwellings were measured at ENEA (Bologna, 324). In a unventilated basement 12 % of the alpha activity is associated with particles larger than 0.35 µm, and 88 % with particles having a median diameter of 0.14 µm. In an office, in moderate ventilation conditions, 23 % of the activity is associated with particles less than 0.045 µm, 21 % with particles between 0.045 and 0.13 µm, 34 % with particles

between 0.13 and 0.35 μm, 11 % with particles between 0.35 and 0.65 μm, and 11 % with particles larger than 0.65 μm.

A great number of field dispersion experiments was carried out (GSU, Hannover, 314). The results demonstrate the inhomogeneities within a dispersing plume due to insufficient turbulent mixing and they indicate how difficult it is to obtain representative samples from the cloud. Investigations have been performed to compare the measured total tracer concentrations in an artificially generated plume with theoretical predictions. In most cases the experimental values were much lower than the theoretical estimations showing differences of up to two orders of magnitude. This must be attributed mainly to the fact that the center of the plume may deviate considerably from the main wind direction. In only very few experiments were the measured concentrations close to the predictions.

2.5. Plant-animal transfer of radionuclides

2.5.1. Purposes

Radionuclides may be involved in two different types of biochemical interactions. Some radionuclides indeed act as tracers for indispensable nutrients and have been isotopically exchanged, bound to and even assimilated in the biosphere. To these radionuclides belong all the isotopes of macro- and micronutrients necessary for the normal functioning of life. Radionuclides, such as e.g. U, Am, Np, Tc, Cs, Rb, etc., however, do not belong to the category of nutrients and their transfer from plants to animals has therefore not yet been well understood.

A few remarkable facts can be elicited from the literature concerning the fate of radionuclides in the biosphere. Tritium has well been investigated in animals but less well in plants. Carbon-14 metabolism is well-known in plants for obvious reasons. Sr-90 and Cs-137 have been used for many years to trace calcium and potassium. Fe-59, Zn-65, Mn-54 and Co-60 are often used in the studies on micronutrients in plants and animals. Speciation of actinides in plants and animals is rather difficult to investigate, particularly because of their limited uptake. Elements like technetium on the other hand are readily accumulated in plants and thus has led to considerable interest in its speciation.

2.5.2. Radionuclide speciation and its influence on the gastrointestinal uptake

The results obtained on gastrointestinal absorption of Np, Pu and Am together with information available from other laboratories have led to NRPB recommendations for gut uptake factors for members of the public ; the increase of the value to 0,01 % for Pu as compared to the currently used ICRP value of 0,001 % for soluble forms takes into account the evidence, although limited, that organic bound Pu in food will be more readily available for

absorption than its inorganic forms. In new-born animals the absorption of Np, Pu and Am is increased by a factor of 100 in the immediate post-natal period falling to adult values by about the time of weaning.

To evaluate the 0.01 % absorption factor of ingested inorganic forms of plutonium, one has also investigated whether some organic Pu complexes could enhance this gut absorption. Some Pu complexes have been therefore artificially induced in potatoes. These complexes and also some chemically produced Pu complexes have been tested in among others rats and rabbits. Pu phytate appeared to be most related to an enhanced Pu uptake. A relation between this enhanced Pu uptake and the phytate-digesting enzyme phytase, present in the small intestinal brush border, was established. Human beings, not having high phytase activity will very probably not show an increased gut absorption when ingesting Pu phytate. Such speciation issues in animals, with their eventual consequences for men, were discussed at Speciation-85, a seminar which took place at Oxford, 1985 (see annex V). An important outcome of the presentations and discussions was the lack of information exist about the speciation of activated corrosion products but also the need for a continuing effort to study speciation mechanisms with a view to setting up appropriate recommendations.

The incorporation and residence time of ingested organically bound tritium (OBT) in milk and in fetal tissues was chosen as a model for tritium behaviour in mammals (LH, Wageningen, 432). Some OBT has been found to be turned eventually into tritiated milk fat, casein and lactose. Incorporation in fetal tissues resulted in levels of only about 0.1 % of the daily dose received by the mother. In young animals, tritium is most rapidly turned over, and after four months only very small amounts of OBT remain in young animals, except in their central nervous system. Similar experiments were done at CEN/SCK (Mol, 431) with studies of both OBT and tritium oxide incorporation. When young mice were fed with OBT an important amount of tritium was incorporated in the brain. A rapid fall in activity was observed when animals were removed from tritium administration. The turnover was the slowest in the brain. When pregnant sows are given tritiated water an equilibrium specific activity ratio of 0.7 results in body water in the mothers or in new-born pigs. This ratio is about 0.14 for organic tritium in most tissues. A detailed biochemical study revealed that tritium labeled lipids undergo relatively rapid dilution when they become incorporated into body lipids. They may therefore represent a critical pathway in the risk from OBT in food.

After intravenous TcO_4^--95m injection of sheep, the highest concentrations were found in the thyroid. A more intensive incorporation in tissues occurs when Tc is given bound to organic constituents in the food. In rats however the Tc bound to algae appears to be less well absorbed. Considerable amounts of Tc also appeared in the wool which may thus constitute an easily

accessible indicator for the extent and age of a contamination by Tc (CEN/SCK, Mol, 467).

Setting up an iodine inventory has continued at GSU (Hannover, 314) examining 14 human and 27 animal thyroid glands. On the average the isotopic ratio I-129/I-127 was 5.10^{-8} for human and 1.5 to 2.0×10^{-8} for animal thyroids. A transfer factor experiment with cow milk fed to a pig yielded a thyroid/feed transfer factor of 6.4×10^{-3}.

3. MEASUREMENT TECHNIQUES

3.1. Purpose

Transfer of radionuclides in the different ecosystems is very much conditionned by their chemical forms. Therefore a continuous effort is necessary to improve techniques needed to identify these forms and their modifications with time. Intercomparison exercises are much desirable to guarantee the preciseness of the analytical methods.

3.2. Determination of radionuclides chemical forms

In order to study the physico-chemical characteristics of radioactive aerosols, a high-flow virtual dichotomic impactor has been made. This instrument allows the collection of information on the harmful effects of different categories of atmospheric contamination by aerosols of differing dimensions (CEA, Fontenay-aux-Roses, 436).

Photoelectron spectrometry was applied to investigate the solid aerosols which are present in the atmosphere of Uranium mines and workshops processing the principal constituents of this metal. Photoelectron spectrometry measures directly, in the solid the binding energies of the electronic levels of the chemical elements. This technique showed that UF_4 leached from an artificial physiological solution was transformed into UO_2 and then into UO_3 (CEA, Fontenay-aux-Roses, 464).

Work on the efficiency of samplers has progressed. The work on the dispersion of aerosols and ventilation patterns has been confined to a general review of the situation, a study of resuspension and a preliminary study of methods for the determination of dispersion. Both computer modelling and experimental scale models appeared very unlikely to provide the data required to describe dispersion of aerosols and to determine the real situation at work (AERE, London, 332).

An extracavity fluorescence apparatus, based on a ionized argon laser has made the measurement of $^{129}I_2$ in an industrial environment possible, with a sensitivity of 5.10^{-11} gcm^{-3} (CEA, Fontenay-aux-Roses, 465).

4. PERSPECTIVES AND RECOMMENDATIONS

The most obvious gaps which have been revealed at the end of the previous contract period may be the source of recommendations for the future research :

Certain aspects of the atmospheric transfer of radionuclides in accidental conditions must be given more attention. Especially the speciation of the radionuclides and their chemical transformation which may occur in the plume, the deposition rate on plant and soil surfaces and the subsequent chemical transformations are all topics for intensified research.

The development of soil-plant transfer models relies heavily on provisional data, especially for long-lived radionuclides. Little attention has been paid so far to the quality of these radionuclides in complicated biogeochemical cycles. Quantitative descriptions of their transfer over long periods are therefore rather uncertain. Microorganisms may also play an important role in most of the ecosystems and even determine the quantities of radionuclides available for transfer.

Some good but incomplete data on the influence of speciation of radionuclides on their gut absorption suggests that more investigations in this direction are needed. It has been proved that changes in the estimations of radionuclide uptake by animals and man may arise when radionuclides have different chemical configurations from the ionic form. However, this has been tentatively assessed for only a very few radionuclides, and more information is needed before general rules can be derived.

Different parameters of biological, physico-chemical and chemical nature form the basis of mathematical equations which describe the transfer through the various ecosystems. They will allow judicious assessment of which countermeasures ought to be taken when inadvertant releases to the biosphere have occurred.

The mechanisms of oxidation of elemental tritium (HT) as well as the behaviour of other H-3 chemical forms when entering the biosphere (soil, plant, animal) remain unknown and need further investigation in view of future developments in the nuclear fusion area.

The potential existence of different contaminating effluents from nuclear power plants, i.e. heat, non-nuclear pollutants and nuclear pollutants, has not sufficiently been brought to light by the previous contracts. A great effort should be made to study their individual impact on the environment but also their mutual interactions, since it has been shown that transfer of radionuclides is not solely governed by their mere content in the substrates. The physico-chemical and chemical insights about interferences from their microenvironment and accompanying pollutants must be improved before reliable mathematical descriptions can become available.

SECTOR C

SHORT TERM SOMATIC EFFECTS OF IONIZING RADIATION

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   2.2. Base damage
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3. Radiation effects on bone marrow and immune system

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4. Radiation damage to skin and underlying tissues

5. Effects of radiation in other tissues
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6. The developing organism
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7. Perspectives and recommendations

1. PURPOSE AND GENERAL VIEW

Damage to the bone marrow can be a consequence of a very rare whole body exposure; damage to skin and underlying tissue can occur after accidental local overexposure. In both cases, one needs to determine the degree of damage and to initiate appropriate therapy; this requires a knowledge of pathogenetic mechanisms. These aspects form a large part of the sector "Short-Term Somatic Effects of Ionizing Radiation". For convenience, changes in these tissues occurring several months and years after exposure are also treated in this context. Early damage also plays an important role in thyroid and the lens of the eye, although the more serious lesions appear much later.

Development of the mammalian organism in utero and during infancy depends on exact timing and interaction of the various steps of differentiation and can become severely deranged by relatively small doses of radiation. Determination of threshold doses and pathogenetic mechanisms has been the principal aim of these studies.

In order to explain the action of radiation on the cell and its descendants, the nature of the radiation-induced changes in DNA, i.e. primary effects of radiation, have also been studied. The chemical nature of these changes and the influence of different agents have been characterized; however, as this subject is too remote from the practical aspects of radiation protection, it has been dropped from the 1985-1989 programme.

2. PRIMARY EFFECTS OF RADIATION ON DNA

2.1. Introduction

The genetic material, DNA, is the major biological significant target for the action of radiation on cells. Once radiation-induced damage to the molecular structure of DNA, its repair and its influence on DNA function are understood, risks from radiation can be much better assessed, predicted and prevented. This is the rationale behind studies on radiation effects on DNA which, otherwise, might appear remote from the practical problems of radiation protection. Considerable progress in deciphering the molecular structure of the genetic material has been made in recent years: new techniques for defining damage in DNA and for characterizing the rapid reactions which take place following irradiation have been developed, and this has markedly advanced research on primary effects of radiation. European research has become a leader in this field due, to a large extent, to the cooperation between the various contractors of the Community's programme. Nevertheless, it has not yet been possible to establish the complete link between the physical processes of absorption of radiation energy and the appearance and reparability of damage in the cell, and one may wish that this goal had been maintained more clearly in focus in some investigations.

Radicals induced in different DNA constituents are the first tangible consequences of the interaction of radiation with living matter. At this stage, damage is not yet fixed and may be reduced or promoted by certain agents. Even after these primary lesions have been transformed to chemical changes such as single and double strand breaks, alterations of bases or crosslinks, it is still possible to avert DNA damage, in part, by enzymatic repair, if accurate. Research on primary effects aims to characterize the initial and secondary free radicals, their conversion to the radiolytic end products in DNA, the modifications caused by oxygen (the oxygen enhancement ratio OER), protective or sensitizing agents and the relation between chemical and biological damage. A wide spectrum of techniques are used in these studies. Since the reactions are extremely rapid they must be retarded by absence of solvents, low temperature, freezing etc. The free radicals are measured and characterized by physicochemical methods such as electron spin resonance (ESR) or their chemical reactivity.

2.2. Base damage

Although radiation can affect all nucleic acid bases, lesions in thymine and guanine appear most important. Such base damage may result in breaks in the continuity of DNA single (SSB) or double (DSB) strands via various secondary reactions. DNA breaks may, however, also arise directly by way of other mechanisms.

Irradiation of deoxyguanosine in the absence of oxygen causes an opening of the imidazol ring due to hydroxyl radical addition at the position of carbon 8 (CEA, Grenoble, 350). Restitution within the purine ring can result in furanoid epimers of the sugars and in base-damage-related release of phosphate. Oxygen prevents the formation of formamido pyrimidines and the rearrangement within the sugar moiety. Indeed, alkali labile DNA breaks have been detected to occur preferentially at guanosine sites.

Halogenated pyrimidines (Univ., Regensburg, 342) included into glasses at a low temperature and irradiated, undergo reductive halide elimination, hydrogen addition or base oxydation dependent on whether the type of glass allows reaction with e^-, $OH^\cdot$ and SO_4^-. The behaviour resembles that observed in aqueous solutions but, due to steric influences, is not quite the same. No indication for base-sugar radical transfer or for breakage of glycoside bonds was found in studies in glasses. Following irradiation of sugars (glucose, ribose, deoxyribose), radicals were found at different carbon sites. These may be different after irradiation in aqueous solution and in glasses.

The transient and final products of the action of radiation on thymidine were defined in cooperation with different groups (Univ., Brussels, 359; CEA, Grenoble, 350; Univ., Leicester, 362). The 5.6 dihydrothymid-5-yl radical can abstract hydrogen from sugar and result in a release of the base. It also can react with water or undergo deprotonization. An important

endproduct of the action of radiation on thymidine is dihydrothymidine. After irradiation at low temperature, the only detectable radicals in DNA in the absence of oxygen are $G^{\bullet +}$ and $T^{\bullet -}$ (Univ., Leicester, 362) both of which can give rise to single and double strand breaks, the latter occurring two orders of magnitude more frequently than expected. This is thought to be due to the fact that $G^{\bullet +}$ and $T^{\bullet -}$ radicals have a high probability of being within a distance of ca 3 nm. On the other hand, attack by indirectly formed $OH^{\bullet}$ radicals is likely to be random. It is therefore concluded that DSB could be mainly due to a direct radiation action.

$H^{\bullet}$ as well as $OH^{\bullet}$ radicals intervene in radiation-induced cleavage of H-3 or C-14 from specifically labelled phage DNA in diluted aqueous solution in the presence and the absence of oxygen, buffers or DMSO (dimethylsulfoxide) (Univ., Münster, 470). Oxygen enhancement was about 3 for tritium cleavage and 5 to 9 for demethylation. Methyl radicals cleaved from bases can react with DNA sugars. Studies on fibres of substituted 5-halouracil indicate that the primary radical species are the anion of thymine and the cation of guanine. Combined effects between radiation and chemicals on supercircular plasmid DNA depend on the buffer system used; the chemicals may act as $OH^{\bullet}$ scavengers independently of their binding or intercalation action on DNA.

2.3. DNA strand breaks

DNA strand breakage can arise from sugar damage or base derived radicals (MPI, Mülheim, 341). Base damage is the principal factor in strand breaks and base release in a poly(U) model system. The oxygen effect is mediated via conversion of radiation-induced radicals to peroxyl radicals and has been measured in nucleotides, polynucleotides and DNA on the basis of O_2 uptake. Only pyrimidine but not purine bases reacts in this way, and oxygen uptake is proportional to pyrimidine content of nucleotide mixtures or small DNA fragments. Higher molecular weight DNA, consumes however more oxygen by mechanisms which need to be elucidated. High molecular weight DNA can be obtained from E.coli following treatment of the cells with a chloroform saturated detergent EDTA solution (MRC, Chilton, 363). This method might have less effect on the structure of the DNA than ethanol inactivation. The plot of DSB in the coli DNA against dose yields a linear function with an intercept (within the range of experimental error) of -1 suggesting that, before the continuity of the strand is disrupted, one break of the circular DNA had to occur. This indicates that DNA has been isolated with very little shearing. Using these two methods of DNA isolation the yield of DSB/genome/Gy for ethanol inactivated cells was about 1.8 times larger than that obtained with the new method using detergents. This may be due to a destabilizing effect of ethanol on DNA near two trans-oriented SSB.

Radiation damage in DNA and the role of protecting agents was studied using pulse radiolysis in conjunction with light

scattering measurements (Hahn Meitner Inst., Berlin, 469). Two modes of changes in light scattering were detected, a rapid one due to the diffusion of DNA fragments and a slow one corresponding to the life time of free radicals at sugar moieties. The latter decay is accelerated by the addition of protecting substances such as cysteamine. It is concluded that DNA strand breakage results from the action of $OH^{\bullet}$ on sugars mediated, perhaps via base radicals.

In fact sugar-centred radicals are elusive and short-lived and have so far only been detected in the presence of iodoacetamide which rapidly removes the longer-lived base radicals (Univ., Leicester, 362). Direct as well as indirect effects may contribute to DNA breaks. Studies on ESR spectra after addition of H_2O_2 suggest that indirect formation of SSB by $OH^{\bullet}$ is not much more important than that by a direct action. In view of data reported below, this may also depend on temperature during exposure.

2.4. Damage to native DNA and biological effects

The molecular damage in chromatin was compared to that in DNA alone (ULB, Brussels, 359). Both electron spin resonance spectra are very similar and are characteristic of H addition to C6 of thymine although DNA represents only half the amount of the total nucleohistones. This observation suggests transfer of radiation energy, probably via released electrons, from proteins to DNA. The final degradation products of radiation action on pyrimidines were characterized as dihydrothymidine and 5 hydroxy-methyl-2-deoxyuridine.

EPR studies using X and gamma rays on chromatin revealed only guanine $G^{\bullet+}$ and thymine $T^{\bullet-}$ but no sugar radicals (Univ., Homburg, 289). An additional broad singlet has been associated with histone radicals. Comparative studies on histones, chromatin and DNA indicate that radicals in chromatin are transferred from histones to DNA. $T^{\bullet-}$ radicals formed are converted by oxygen to peroxy or thymyl radicals by reaction with protons. The former reaction predominates at temperature above 180°K, the latter reaction at lower temperatures.

Damage from gamma radiation may not be randomly distributed along the DNA chain. This was studied in aqueous DNA solutions, in lambda phage and in yeast cells using enzymatic analysis and base pairing (GSF, Neuherberg, 343). After in vitro exposure, damage appeared randomly distributed over the chain as a result of indirect action by water radicals. After in vivo exposure, however, local denatured regions were identified containing several base damages, apurinic sites and strand breaks. Such denatured regions had about twice the frequency of DSB and correspond to about 50 to 100 bases. In UV irradiated phage, such clusters were also observed and appeared as local expansion of pyrimidine lesions.

DNA from coli phage ØX174 was used to study the relation between biological activity and primary damage (Univ., Amsterdam, 356). Freezing protects DNA from Co-60 gamma radiation damage but the extent depends on the speed of freezing. A considerable portion of rapidly frozen DNA is radiosensitive perhaps due to changes in the microenvironment of the DNA molecule. The oxygen effect also depends on temperature during radiation and the rate of freezing. The sensitivity of single strand DNA irradiated even at -196°C (under anoxic conditions) is considered too large as to be explainable by direct action alone, and the oxygen effect is considered to be due to O_2 electron traps in the immediate environment of DNA.

Radioactive nuclides incorporated into DNA upon their decay can cause very specific damage dependent on recoil energy. This was studied (Inst. Curie, Paris, 349) using the 2 phosphorus isotopes P-33 and P-32 incorporated into the single stranded S13 phage or the double stranded T2 phage. In contrast to P-32, the low recoil energy of P-33 cannot cause a break. In single stranded phage, P-32 results in identical dose effect curves for breaks and lethal effects whereas P-33 can be lethal without destroying the circular integrity.

2.5. Effects of modifiers

Oxygen has long been known to sensitize cells to the action of ionizing radiation, the so-called oxygen enhancement ratio (OER). The mechanisms at the molecular level are, however, not yet clear because oxygen may intervene at different points in the chain of events leading to cell death, and because radiochemical changes in DNA can have an OER for DNA different from that for cell death. Certain groups of compounds, for example those containing SH groups such as glutathione, protect against damage whereas others for example nitroimidazoles, sensitize.

The interaction of $OH^{\cdot}$ radicals with DNA bases and the different reactions of the resulting oxidising and reducing adducts were studied by pulse radiolysis and rate constants have been determined (MRC, Chilton, 363). The action of reducing agents with $OH^{\cdot}$ adducts proceeds via electron transfer and may result in a restitution of the biomolecule via dehydration induced by $OH^{\cdot}$ radicals of the resulting product or via $OH^{\cdot}$ elimination, thus demonstrating potential repair of DNA radicals in bases via reductants. Thiyl radicals are formed in this process may interact to repair indirectly radicals resulting from H atom abstraction (sugar-phosophate radicals). Interactions of oxidizing $OH^{\cdot}$ adducts with oxidants seem to be inefficient; that concerns also reaction with oxygen. Thus, depending on the redox properties, protection as well as sensitization may occur by thiols and reductants.

The reactivity of different oxyl radicals was studied to obtain information on potential targets of organic oxygen radicals (GSF, Neuherberg, 343). Alkoxyl radicals were found to be short-lived and very reactive, peroxyl radicals had a longer life span. DNA can also be inactivated by oxydizing fatty acids, a theory

proposed by ALPER. Model studies showed that damage may occur from oxidized products, but protection effects by low concentration of polyunsaturated fatty acids were also observed.

In the presence of oxygen, $O_2^{\cdot -}$ radicals are formed at the expense of $T^{\cdot -}$ radicals but since $RO_2^{\cdot}$ radicals are also formed from $T^{\cdot -}$ and $G^{\cdot +}$ only a slight increase in SSB and DSBS results (Univ., Leicester, 362). Glutathion (GSH) is often thought to repair radiation damage by hydrogen donation and thereby to enter in competition with oxygen. Another mode of action proposed involved repair of $T^{\cdot}$ radicals by forming $SH^{\cdot}$ radicals (Univ., Leicester, 362). Model experiments on dilute protein and DNA solution indicate, however, that GSH acts directly on biomolecules via the radiation-induced GSO_2 radical (ENEA, Casaccia, 441). This is also shown by experiments on bacteria, in which depletion of GSH with buthionine sulfoxime (BSO) increases oxic as well as anoxic lethal radiation damage. Comparison of the oxygen effect for cell killing, mutation and DNA strand breakage in a mammalian cell line suggests that cell killing and mutations are related but both apparently do not depend on DNA strand breakage.

Reduction of intracellular GSH by BSO resulted in only a small sensitization with respect to cell killing, SSB and DSB under hypoxic or anaerobic conditions; this sensitization against SSB and DSB was much larger at intermediate oxygen concentrations indicating that SH compounds protect mainly against oxygen type damage (TNO, Rijswijk, 403). When BSO treatment was continued for several generations, dose effect curves for cell killing of hypoxically irradiated cells approach those obtained anaerobically but repair was significantly affected (GSF, Frankfurt, 394). Probably, changes in several intracellular pools related to protein and non-protein bound GSH may be involved in this complex response.

Rapid mixing techniques have been used to study the kinetics of the action of protecting agents (DMSO and cystein) on V799-7538 cells (MRC, Chilton, 363). These cells which have OER of 2.8 are protected only when the $OH^{\cdot}$ radical scavenger DMSO is present during or shortly after irradiation, and the kinetics for DMSO is determined by diffusion processes. This behaviour resembles that of radiosensitizers. In the case of thiols much longer contact times (>1 second) with the cell are required and other effects, for example on the membrane, may play a role under the conditions of the experiment.

Membranes could be another point of attack for radiation perhaps related to DNA damage. Radiosensitivity depended on lipid composition of cell membranes in a mycoplasma strain, being lower when unsaturated fatty acids are present (MRC, London, 361). Apparently peroxidation of membranes does not play a role in radiosensitivity under these conditions. Although in vitro peroxidation could be induced in such a fatty acid mixture, this could not be found in intact mycoplasma. Mammalian lymphoid cells grown in the presence of an excess of non-saturated fatty

acids showed marked changes in the composition of their cellular membrane but not in that of their nuclear membrane and this may explain why their radiosensitivity was unaltered by this treatment.

3. RADIATION EFFECTS ON BONE MARROW AND IMMUNE SYSTEM

3.1. Introduction

When large parts of the body are exposed to radiation doses above 1 Gy, bone marrow becomes the critical system for radiation symptoms since its stem cells need to divide at a high rate to maintain an adequate number of blood cells, and since it is widely distributed throughout the body. The bone marrow syndrome preoccupied radiation research for many years until it became progressively apparent that such accidents are very rare.

Since such accidents can, however, have very serious consequences, they must be prepared to treat them, for example, by means of bone marrow transplantation. Moreover, smaller doses applied over longer periods of time may also damage the bone marrow and immune system because of their limited capacity for repair. Studies of the mechanism of the damage to these systems and the relation between their failure and leukaemia development are therefore carried out.

3.2. Bone marrow transplantation

Bone marrow transplantation (BMT) is a potential life-saving treatment when large parts of the body are exposed to doses of more than 5 to 6 Gy. Crucial problems involved in bone marrow transplantation are:

a. transplanted marrow may not take since the remaining immunological capacities of the host destroy the graft (host vs graft reaction).
b. secondary disease may occur when donor-derived lymphocytes engender an immunological reaction against the host's tissues (graft vs host disease GvHD).
c. late effects may arise as a result of the action of radiation on tissues other than the bone marrow (e.g. the lung).

These problems are progressively being solved and, as a spin-off, extensive irradiation with doses of 10 Gy and more followed by matched bone marrow transplantation (MHC) has become valuable in the treatment of leukaemia and bone marrow aplasia. After accidental irradiation one must cope, however, with the additional problem that the dose and its distribution in the body are uncertain and it may be difficult therefore to decide whether a transplantation will be possible and beneficial. Beside an assessment of the physical dose of radiation, biological indicators of radiation damage might be useful in such a situation.

GvHD has been studied extensively in experimental animals and in man since a perfect match of the transplant may not be possible, particularly, following an accident. Three approaches to avoid or mitigate GvHD have been pursued:

a. removal of immunocompetent cells from the graft by physical or immunological means,
b. post-transplantation treatment of the host with immunosuppressive agents,
c. elimination of factors triggering GvHD.

3.2.1. Preparation of bone marrow grafts

A sufficient number of viable stem cells with minimal contamination by immunological active cells is needed for transplantation. Sources of stem cells other than the bone marrow may be more readily available or may involve less risks (Univ., Ulm, 345). Blood contains a small number of stem cells whose number can be increased by previous treatment of the organism with dextran sulfate. Such autologous stem cells from dog blood are as efficient as those from marrow if related to an equal number of granulocyte macrophage progenitor cells. Blood stem cells found in greater number during the overshoot phase after chemotherapeutic treatment proved, however, to be less suitable. Cryo-preserved stem cells from fetal liver repopulated rapidly the marrow of irradiated dogs, and the absence of mature T cells in the transplants reduced GvHD incidence; however, mismatched fetal grafts did not take well from a long term point of view, and radiation-induced pancreatic fibrosis was a major problem.

If the donor cannot be well matched to the host, an attempt may be made to remove as many immunological reactive cells from the graft as possible. Polyclonal and monoclonal antibodies against lymphocytes were incubated with allogenic marrow which then was transfused to irradiated mice (GSF, Neuherberg, 344). Monoclonal antibodies were found much less effective in preventing GvHD than a polyclonal antibody against thymocytes, with one exception, which interestingly did not require complement for its action.

There is a certain risk involved in removing all T cells from donor marrow since these cells eliminate residual immunological defenses of the host, and their removal may jeopardise engraftment. Using hemopoietic recovery of irradiated rhesus monkeys after autologous stem cell transplantation as a test, it could be shown (TNO, Rijswijk, 535) that pretreatment of the cells with a mixture of monoclonal or polyclonal antibodies did, in general, not affect their effectiveness. A reduced recovery was, however, observed when the cells had been treated with a pool of antibodies directed against HLA-DR antigens. Monkeys receiving untreated allogenic transplants died rapidly from GvH. If the graft had been treated with antibodies against all lymphocytes (CAMPATH-1) a slight improvement in lifespan and severity of GvHD was found but not if it had been treated with

antibodies against certain subpopulations. Another antibody against the E-rosette receptor also showed some promise.

Bone marrow cells may be fractionated in an albumin gradient to remove immunocytes (Univ., Ulm, 345). Although this reduced GvH in only slightly mismatched transplants of dogs it was ineffective if the mismatch was more severe. Lymphocytes have also been removed by density centrifugation and E-rosette depletion from grafts of rhesus monkey (TNO, Rijswijk, 357). It has been shown that more than 99.9% of the lymphocytes have to be inactivated or removed in order to prevent GvHD.

Removal of immuno-competent cells, although still not yet completely successful, has greatly improved the success rate of bone marrow transplants and is now used worldwide in the treatment of hematological disorders. It should be emphasised that this approach has been initially developed for man, in contracts of the Radiation Protection Programme.

3.2.2. Treatment of the patient

Immunodepressive agents might be used to prevent graft rejection and GvHD; they may also serve as a model to study damage to the immune system. Studying a great variety of immunosuppressive agents (Inst. Mario Negri, Milan, 355) it was found that each compound had a different characteristic response with respect to natural resistance mechanisms (e.g. natural killer cells, NK) and expression and regulation of immunity (macrophage cytotoxicity, macrophage-mediated non-specific and T-cell-mediated antigen specific suppression). Even closely related compounds may have very different modes of action, and a given compound may enhance one type of immune cell and suppress another one. These observations open up possibilities for a more specific treatment of immune disorders. New immunodepressant proteins with specific action on various immune cells have also been isolated from plants. Since these proteins are not very toxic they have interesting therapeutic potential. In other studies, treatment with cyclosporin A prevented or reduced substantially GvHD in DLA-matched transplants; it seemed less effective in other combinations (TNO, Rijswijk, 357).

Secondary disease can be triggered by microbial antigens and might thus be prevented by decontamination of the gastrointestinal tract (TNO, Rijswijk, 357). This has been studied in irradiated rhesus monkeys given different types of mismatched grafts whose T cells had been partly removed by gradient centrifugation. A stage of gnotobiosis in the recipient appeared beneficial only when the number of transplanted T cells was small, and GvHD due to addition of T cells to the graft was only postponed but not prevented by decontamination of the recipient. Parallel studies indicated that the number of T cells which lead to GvHD in decontaminated mice depended on the degree of mismatching, GvHD being best avoided if the H2 antigen was compatible. None of the microbial species studied seemed to be solely responsible for triggering GvHD.

3.3. Late effects and recovery

The repopulation of lymphatic tissues by T cells after irradiation and bone marrow transplantation was followed by immunohistochemical methods (GSF, Neuherberg, 344). Bone marrow deprived immunologically of T cells apparently contains precursor cells which mature under the influence of an incompatible thymus and repopulate postthymic T cell areas. Xenogenic bone marrow grafts of mouse in rats were achieved by strong immunosuppressive preconditioning with antithymusglobulin. Surviving rats exhibited marked chimaerism in hemopoietic cells but not in lymphocytes, rejected mouse skin grafts and suffered from GvHD after injection of mouse spleen cells.

Short and long term consequences of radiation were studied in dogs given cryo-preserved autologous bone marrow after single and fractionated irradiation (GSF, Neuherberg, 344). Fractionated over a week, a dose as high as 22.5 Gy could be tolerated by half of the animals, and survival was improved by non-absorbable antibiotics. Optimal results were obtained when 10^8 autologous bone marrow cells were transplanted. If fractionation time was reduced, and/or single doses were increased, mortality from the gastrointestinal syndrome became important. Delayed mortality over a period of up to 8 years occurred, in that order from infections, malignant tumours, (auto)immune diseases and interstitial lung fibrosis. Disturbance of pancreatic function and fibrosis is probably responsible for weight loss in survivors. Acute survival after transplantation of partially mismatched marrow (from litter mates) was poor after single exposure; it could be improved by fractionation (provided no hyperfractionated regimen was used) and by methotrexate and antibiotic treatment, but late death from GvHD could not be prevented. Immune reconstitution was studied in rhesus monkeys (TNO, Rijswijk, 357).

The influence of dose, dose rate and radiation quality (fission neutrons against Co gamma rays) was studied with respect to the hematological syndrome in rats (CEA, Fontenay-aux Roses, 346). Reticulocytes in the blood followed by platelets and lymphocytes reflected best the function of the bone marrow. An increase in dose rate from 0.1 to 10 Gy/hr increased damage only slightly, fractionation into daily doses for 0.6 to 1.22 Gy reduced the effect by a factor of 2 to 2.5. The RBE for life shortening increased from 3 to 15 for high doses and dose rates to 15 for the low dose and dose rate. The RBE for tumour induction was 35 and essentially independent of dose. If the dose is expressed in Sievert, both types of radiation yielded the same dose effect curves and the same distribution of tumours.

3.4. Clinical observations after bone marrow transplantation in man

Studies on a patient who had been treated by whole-body irradiation followed by bone marrow transplantation can provide valuable information on the consequences of such a therapy after

an accident. The International Bone Marrow Transplant Registry (IBMTR, Milwaukee, 471, 520) keeps track of clinical data and success of bone marrow transplantations all over the world (with a strong participation of European scientists). It thus constitutes a precious data base for the treatment of eventual accidents. The progress in clinical applications of bone marrow transplantation is largely based on radiation protection research such as enumerated above. The number of transplantations reported to the IBMTR has increased greatly, 1,821 new transplants and 50 new teams have been entered into the data base since July 1982. Applications of clinical BMT following therapeutic irradiation are mainly: acute myelogenous leukaemia, acute lymphoblastic leukaemia, aplastic anaemia and immunodeficiency. The percentage of successful transplantations has also increased. Late interstitial pneumonitis after irradiation and transplantation remains a difficult problem, however, and the role of radiation and virus in its genesis remains unresolved.

Early and late effects were studied in persons exposed to radiotherapy of large parts of the body. Vomiting soon after irradiation is a serious handicap after total-body exposure of patients and occurs when a single dose exceeds 2 Gy; it can be reduced by rest and a combination of steroids and barbitone (Royal Marsden Hosp., Sutton, 448). Vomiting and nausea also represent a sensitive sign for exposure to a potentially hazardous radiation dose. Vomiting seems to occur to the same extent after exposure of the lower and upper part of the body and may occur either via a direct effect on the vestibular apparatus or via an action on the gastrointestinal mucosa. Renal function late after irradiation was found to have been affected only in patients suffering from GvHD. Exposed women suffer from ovarian failure and require hormonal treatment. In children puberty fails to occur and growth is impaired. Pneumonitis, partially caused by cytomegalic virus or pneumocystis carinae is a critical factor in the long-term survival of such patients, lung function, particularly diffusion capacity abnormal for several years, but at late times, some trend for improvement was noted.

3.5. Consequences of lower doses or of continuous irradiation

Single or repeated exposures which do not result in overt bone marrow syndrome take place more often than massive accidents and may cause longlasting latent damage. In the search for a reliable indicator of bone marrow function, different types of stem cells (granulocytemacrophage culture forming cells GM-CFC and burst forming erythropoietic cells BFU-E) were cultured in vitro after irradiation of dogs and man (Univ., Ulm, 345). After whole-body exposure of dogs to 0.19 Gy, blood CFC values returned to normal within a month. After 0.79 or 1.57 Gy, only 50% of control levels were attained after 5 months. Fractionated exposure caused a similar long-term defect. Bone marrow at different sites of the body is linked by various regulatory functions. If all marrow in irradiated foreparts of dogs had been destroyed it recovered from seeding from non-irradiated

hind-parts with considerable delay. This recovery was accelerated when the hitherto non-irradiated part of the dog also was irradiated. Misregulation of marrow activity and not stromal defects must thus have been responsible for the delay. These studies suggest that bone marrow recovery might be promoted by treatment of persons exposed to partial body radiation. The behaviour of GM-CFC and BFU-E was also studied in patients treated with radio-iodine for thyroid carcinoma or adenoma with iodine. These culture techniques also allowed the determination of the in vitro radiosensitivity of human stem cells from bone marrow and blood.

The response of bone marrow to repeated low level exposure was studied (Univ., Ulm, 345) in cooperation with Argonne National Laboratories (USA). Dogs exposed daily (5 days/week) with 19 mGy/day showed the most dramatic changes in hematology during the initial phase until about 3 Gy were accumulated. Granulocyte (but not lymphocyte) values then stabilised at about 60% of controls, and an enhanced rate of proliferation compensated for loss until a dose of about 32 Gy was accumulated. Some animals then developed marrow aplasia whereas others died late of myelogenous leukaemia. Formation of megakaryocytes displayed corresponding changes, and colony stimulating activity in serum increased during the early phase and returned to normal later. More rapid decompensation occurred at daily doses of 38 or 76 mGy, but again the erythroid lineage seemed to stand up best. Bone marrow fibrosis became apparent from 38 Gy, leukaemic cells could be found in all dogs exposed to 38 mGy/day after about 39 to 79 Gy; leukaemic infiltrations were seen in a few dogs on 76 mGy/day already after about 29 Gy.

3.6. Regulation of bone marrow function

The cell replacement system of bone marrow must be able to respond rapidly to varying demands due to infection, blood loss, etc. Humoral and probably intercellular and nervous regulations are thereby involved and much progress has been made in recent years to define the concurring agents and mechanisms of actions. Obviously, this knowledge will be of use when irradiation has strained the resources of the cell replacement in bone marrow.

Several glycoproteins intervene in the regulation of hemopoiesis, the granulocyte macrophage stimulating factor (GM-CSF), the burst promoting factor (BPF), the stem cell activating factor (SAF) and perhaps also interleukin III (IL) (Univ., Naples, 353). Cell lines were isolated which produce these factors in significant amounts and attempts were made to isolate and characterize these factors in cooperation with (TNO, Rijswijk, 357). In cooperation with the Rijswijk group chromatographic and immunological studies and studies on cell systems suggest that SAF, BPF and IL III are identical.

The role of stromal cells on growth and differentiation of bone marrow and thymus cells was studied by in vitro culture (Regional Hospital, Galway, 433). Stromal cells cannot replace specific

factors such as GM-CFS or erythropoietin in supporting long-term growth and differentiation of bone marrow cells. Optimal conditions for culturing human thymus cells, e.g. presence of zinc, were also investigated.

3.7. Biological indicators for radiation damage after whole body irradiation

Among the biological indicators which allow a distinction into categories of radiation damage, cytogenetic techniques are most sensitive and probably also most reliable (see Sector "Genetic Effects of Ionizing Radiation") but they are time consuming and demand considerable experience. Immunological differentiation of lymphocyte subpopulations, eventually using flow cytometry, may allow a more rapid test for radiation damage (BGA, Neuherberg, 518). So far only data on viability after in vitro irradiation have been obtained which indicate that T and B cells are more radiosensitive than "null" cells. Biochemical determinations have been less successful in the past but new techniques, such as isotachophoresis, allowing the simultaneous measurement of a large amount of urinary constituents (INSERM, Paris, 511) have become available. Using this method in whole body irradiated patients, a specific increase in certain constituents, perhaps consisting of peptides, was noted.

Serum from irradiated mice added to a cell culture reduces uptake of iododeoxyuridine due to its increased thymidine content which competes with the radioactive nucleoside (KFZ, Jülich, 288). The effect is transitional and best observed 4 hours after exposure; it occurs in mice already after a dose from 0.01 to 0.1 Gy and less and appears to result from a temporary inhibition of thymidine kinase perhaps by way of an action of intracellular radicals as indicated by studies using different radiosensitizers and radioprotectors. Attempts to use this system in man have not been successful so far due to the much lower level of thymidine in the serum of man than in that of mouse. However, this system has given much insight in as yet unexplored mechanisms of the action of radiation.

3.8. Radiation effects on the immune system

The ability of radiation to destroy immune cells and to cause damage to the immune reactivity of the organism has been known for a long time. Modern techniques allow the study of the role of different cell populations in more detail. While high radiation doses result in a non-selective destruction of all types of lymphocytes, doses, in the order of about 0.5 to 2 Gy, affect primarily unprimed helper cells (ENEA, Casaccia, 354). Defects in these cells are still detectible 3 months after 2 Gy, and complete recovery occurred only 6 months after 4 Gy exposure. Recovery can be accelerated by treatment with the polypeptide hormone thymosine a1; a single injection given 4 days after 2 Gy completely restored helper T cell activity. Helper cells primed by an antigen consist of 2 populations with different functions and radiosensitivity. Irradiation can give rise to an imbalance

between these populations, and this may result in changes in the affinity of antibodies and/or contribute to immune disfunctions. Suppressor cells which specifically reduce the reaction against an antigen become more radiosensitive as animals age; this might explain certain changes in immune functions with age and after irradiation and might be related to the appearance of autoimmune diseases.

The different types of B lymphocytes in spleen, lymph nodes and intestine react in characteristic ways to irradiation (UCL, Brussels, 350, 512). This was studied by immunohistochemical techniques. Non-circulating lymphocytes in the marginal zones of the spleen showed a stronger and longer lasting depression after an acute irradiation than cells in the folliculi. Such a greater sensitivity of marginal cells was also seen after protracted low dose irradiation. Marginal cells also appeared most radiosensitive. As an interesting by-product of these studies, rat hybridomas of immunocytoma cells have been developed from which a series of monoclonal antibodies against human normal and cancerous cells could be obtained which already have been proven useful for diagnostics and therapeutics.

Doses in the range of 0.1 to 1.5 Gy, beside destroying many B lymphocytes, affect the homing process and damage severely precursors of suppressor T lymphocytes (ULB, Brussels, 359). On the other hand, memory suppressor cells are very radioresistant. This imbalance between different lymphyocyte populations together with a release of self antigens from damaged cells can result in autoimmune reactions. Thus, normal immune cells transferred into irradiated recipients lose the ability to express the recurrent idiotype while they continue to maintain their response to arsonate. Such a lack of the suppressing activity of idiotypes could result in autoimmune responses.

3.9. Conclusions

Considerable progress has been made in the understanding of the factors leading to graft vs host disease following bone marrow transplantation. Treatments to reduce incidence or severity of GvHD have been improved. However, there still exists some need to improve the success of transplantation if the donor and host are not well matched. Progress has also been made in the understanding of how smaller doses affect the bone marrow and the immune system. From the point of view of radiation protection, this aspect is certainly as important as that concerned with large doses. One still needs, however, more reliable methods to assess the damage to the marrow and the risks of leukaemia from lower doses and/or continuous radiation exposure.

4. RADIATION DAMAGE TO SKIN AND UNDERLYING TISSUES

Skin had been the first tissue in which radiation damage had been observed; it is still the one which most often is afflicted by accidents. While such local accidents are usually not life-

threatening they can cause severe suffering and disability and require treatment which may be conservative or surgical dependent on dose and dose distribution. The choice of optimal treatment soon after irradiation is not easy and must be based on an assessment of the remaining functional capacity of skin, underlying tissues and especially the vascular systems. The search for indicators of skin damage therefore occupies a considerable part of the programme in addition to studies dealing with the mechanisms of late effects and their dependence on dose and dose distribution.

Early and late radiation effects were followed in pig skin after X-irradiation (Univ., Oxford, 382). The two target populations in skin, the epidermal basal cells and the dermal vasculature are thought to be responsible for the first and second wave of reaction after 4-6 and 12-16 weeks respectively. Fractionation showed characteristic differences in response. Short term recovery was similar for both systems. Intermediate recovery over a few weeks was more rapid for epidermal than for vascular damage. The reactions depend, however, on the species; the second vascular response was not seen in young adult rats, and in contrast to pigs, radiosensitivity of rat skin depended on the age of the animals.

The consequences of non-uniform exposure of skin were studied in pigs using beta radiation sources of different diameters and penetration consisting of strontium-90, thulium-170 or promethium-147 (0.225 Mev) (Univ., Oxford, 382). The dose at which 50% of the irradiated fields displayed moist desquamation increased from about 27 Gy for fields of 22.5 mm in diameter to 450 Gy for fields of 1 mm in diameter. For a given field size it also increased with the penetration of the beta rays.

Wound healing in skin (Univ., Oxford, 382) is severely affected by radiation and this has practical application for the surgical treatment of radiation accidents as well as for situations where radiation occurs combined with other injury. Skin flaps, whether involving or not muscular tissue raised from irradiated skin had lower survival than those from normal skin and this was also reflected by measurements of technetium clearance. Separate irradiation of the entire flap or of its base only indicate that this is due to damage of small dermal and subcutaneous tissues rather than to that of larger vessel.

A large amount of information has been collected on clinical symptoms and treatment of accidents involving acute localized irradiation in man (Inst. Curie, Paris, 348). Thermography allows to detect hyperthermia shortly after exposure and long before clinical symptoms arise although physiological fluctuations and sometimes unavailablity of suitable reference areas limit the usefulness of this method. Vascular scintigraphy after injection of radionuclides and capillaroscopy have also been employed to study vascular functions. Biochemical markers of inflammation, such as acute phase proteins have been assayed, and cultured hair follicles were evaluated for chromosome

aberrations and biochemical alterations to be used as potential biological dosimeters. Success of surgical treatment with pediculate flaps was most successful when carried out after the initial acute phase and prior to the late phase of necrosis.

These studies were assisted by experimental investigations in pigs irradiated locally with gamma rays (CEA, Fontenay-aux-Roses, 347). Early diagnosis and prognosis is crucial to initiate adequate therapy. Indeed, if radiation burns induced in pigs by 84 or 64 Gy gamma rays were excised within 2 weeks, wide-spread necrosis and fibrosis could be prevented. Treatment with anticoagulants reduced early but not late effects whereas anti-inflammatory drugs and agents reducing platelet aggregation also diminished late fibrotic reactions. Micro wave thermographic and thermal conductivity measurements allowed to separate to a certain extent the visible epidermal reaction from damage to the deeper vessels in muscle which is primarily responsible for the spreading of necrosis and later of fibrosis.

5. EFFECTS OF RADIATION IN OTHER TISSUES

5.1. The thyroid

The thyroid is a critical organ when iodine radioisotopes are liberated during accidents. Principal consequences to be considered are atrophy with myxedema, adenoma and cancer. These effects depend however also on regulating factors.

The committed dose from oral iodine-131 intake as quoted by ICRP has been recently called in question and might be only about half as large as supposed. New calculations (Coll. Technol., Dublin, 364) based on improved measurements of the size of the thyroid cell, the follicles and the follicular interspace indicate that an incorrect value for the ratio follicle to gland mass had been used. Both errors almost compensate for each other so that the values of ICRP remain valid.

The effects of radiation and the influence of regulatory factors have been studied in cultured follicular cells from dog thyroid which react specifically to TSH stimulation by changes in morphology and protein synthesis, probably mediated via cyclic AMP (ULB, Brussels, 360). In vitro studies on human thyroid cells have confirmed that follicular cells in normal adults are only renewed rarely (1 in 8 years). Biochemical studies in human thyroid adenomas in parallel with normal tissues from the same patients indicate that such nodules are formed from a single cell which may have undergone a mutation in the iodide autoregulation.

Cultured sheep thyroid cells displayed a D_0 of 2 Gy and an extrapolation number in the range of 2 to 10, with respect to survival after gamma irradiation (Coll. Technol., Dublin, 364). Exposure to iodine-131 is about five times less effective than that to gamma rays. The dose effect relationship is not well reproducible for higher doses above 15 Gy and appears to show a

plateau. Human thyroid cells are more radiosensitive than those of sheep with a Do in the order of 1 Gy and an extrapolation number of about 1.2 and apparently show no recovery after fractionated exposure.

A cooperative group has been initiated (ULB, Brussels, 360) to follow up patients whose thyroid has been irradiated for medical reasons from external sources between 1950 and 1970. A protocol for an intercentre recall programme has been agreed upon, and data is now being collected. A similar protocol is being elaborated for patients who had received high diagnostic doses of iodine-131.

5.2. The lens of the eye

Cataract formation is a non-stochastic effect with relatively low threshold dose and a high quality factor for neutrons. Relatively little work is carried out in the Community on this subject. One contract (INSERM, Paris, 351) dealt with molecular mechanisms of cataract formation in embryonic lens cells. DNA repair proceeds rapidly in 11 day old embryonic lens cells but is markedly reduced in cells kept in culture for longer periods of time. Expression of crystallin formation was not altered 1-3 days after irradiation of an 11 day old lens culture but later underwent modifications. Cycloheximide which delays DNA breakage has no effect on crystallin formation. Endodeoxyribonuclease intervenes in the lens epithelial terminal differentiation, and it is suggested that the high sensitivity of lens cells in the germinative zone of the lens results from an activation of this nuclease destroying sensitive sites of chromatine.

Micronuclei are formed after irradiation of mouse lenses with very low doses (ENEA, Casaccia, 298) and the RBE for 1 MeV neutrons in relation to Co-60 gamma rays was as high as 70 at 2.5 mGy.

6. THE DEVELOPING ORGANISM

Studies on the developing organism concerned embryos cultured in vitro during the preimplantation period, on the central nervous system after prenatal irradiation and on the haemopoeitic system after postnatal irradiation.

6.1. Studies on embryos

The mouse embryo cultured in vitro represents a useful radiobiological model for studying the consequences of radiation on division and differentiation and for estimating the radiation risks during the preimplantation period. Moreover, it appears now that the damage introduced during the preimplantation period may not only lead to very early abortions but also be transmitted to foetal and postnatal life, and this now needs to be studied in more detail.

Induction of chromosome aberrations and micronuclei by neutrons was studied in two cell embryos exposed at different times of their G2 period (Univ., Essen, 290). Proliferation was reduced, and micro nuclei and chromosome aberrations were induced depending on dose. The number of micronuclei increased with time to the blastocyst stage since new chromosome aberrations are generated during the following cell generations. However, there is no quantitative relation between number of chromosome fragments and micronuclei.

The radiosensitivity of the embryo during its early development stages varies greatly. Embryos cultured from mice irradiated at different times after conception showed lowest radiosensitivity if exposed at 24 hours post conception (during DNA synthesis) and highest radiosensitivity at 20 hours (LD_{50} about 0.5 Gy). Mortality occurred during the one cell stage; surviving embryos then developed to the morula stage when mortality again became prominent. The chromosome aberration rate induced in male and female nuclei was about the same. This finding argues against a dependence of radiosensitivity on nuclear volume since female cells have about twice the nuclear volume of male ones.

The reasons why exposure of an early cleaving egg causes death whereas that at a later stage does not affect blastocyst formation were studied using inhibitors of DNA synthesis (ULB, Brussels, 359). Blastocyst formation as well as the "precavitation surge" of DNA and RNA synthesis are dependent upon achievement of the fourth DNA replication cycle but some other differentiation processes occur earlier. On the other hand, trophoblast differentiation is not determined by a particular DNA replication cycle.

Due to the short range of its beta particles tritium incorporated into organic constituents of the cell can cause damage dependent on its vicinity to critical structures of the cell. This has been studied in cooperation (Ispra Biology group and Univ., Galway, 494) using developing mouse embryos supplied with different precursors. Toxicity of such tritiated compounds varied greatly dependent on their ability to be transported in the cell and to be incorporated in or near radiosensitive structures. At 70 hours development, toxicity of arginine and tryptophan was highest followed by thymidine, lysine and histidine. Toxicity of tritiated acid amino acids such as glutamic and aspartic acid was by an order of magnitude less than that of tryptophan. Fractionation of proteins suggests that the high toxicity of tryptophan is related to its incorporation into a compound bound to DNA.

6.2. Effects during foetal and postnatal development

Follow-up of persons irradiated in utero during the atomic bomb explosion confirms that, during a certain phase of development coinciding with the division of neuroblasts, the human brain is extremely susceptible to damage leading to mental deficiency in

later life, and threshold doses may be low enough to be attained by medical diagnostics.

Rats exposed in utero prior, during or after division of neuroblasts were studied at different times of life (CEN-SCK, Mol, 378). Following prenatal irradiation with 0.45 Gy, the brain at adulthood was smaller and displayed a reduced thickness of the cortex. The glia cells were smaller and more densely packed. Studies of biochemical parameters of brain function (biogenic amines, lipids and biochemistry of endothelial cells) were carried out at the same time as the morphological investigations. It appears that mainly the function of nervous cells at adulthood is affected after prenatal exposure since changes were observed in neurotransmitters (biogenic amines and certain amino acids) but not in lipids or endothelial functions.

Infant mice display a greater mortality when a dose is fractionated than when it is given in one exposure (CEN-SCK, Mol, 378). This is due to the fact that radiation during infancy causes an earlier differentiation of radioresistant foetal haemopoietic stem cells to radiosensitive adult ones, and that consequently the second irradiation encounters a more sensitive organism. This sensitization follows a partial depletion of haemopoietic stem cells and can also be elicited by cytostatica. Fractionation is also more effective in causing thymic lymphoma and aplastic anaemia during the first year of life. (For the effects of perinatal alpha irradiation on bone marrow stromal cells, see Sector "Late Somatic Effects of Ionizing Radiation").

7. PERSPECTIVES AND RECOMMENDATIONS

The alterations of the DNA molecule have been better characterized, and the influence of different factors such as oxygen tension presence of sulfhydryl compounds has been defined. These studies although very interesting from a scientific point of view could not yet establish close links to the problems of genetic damage and carcinogenesis on the one hand and to dose-effect relationship and influence of radiation quality on the other and are being abandoned by the programme.

The effects of radiation on the haemopoietic system have been studied intensively for many years, and contractors have contributed essential work on bone marrow transplantation which also yielded important spin-offs for medicine. While there is a need to maintain competence with respect to the treatment of radiation accidents in the Community, this subject is reduced in view of the rarity of accidents involving large parts of the body and of the fact that many of the problems involved have been solved. Studies of late effects in the haemopoeitic and immune system following small and/or repeated doses have given new insights in the relation between non-stochastic damage and leukaemia or the role of radiation-induced immunological deficiencies. These aspects need further attention for the protection of workers.

The study of accidents involving local irradiation to skin and underlying tissues has been carried out on a theoretical and practical basis. More information, especially on early indicators of damage and on the dependence of damage on the tissue involved and radiation modalities is required, and the treatment of such accidents needs to be improved.

Little work is currently being carried out on radiation cataract, and more information on its risks is desirable.

Recent information on brain damage in survivors irradiated in utero at Hiroshima and Nagasaki emphasises the need for a better understanding of the threshold doses and mechanisms for these changes. This is a field which requires much more attention in the future.

SECTOR D

LATE SOMATIC EFFECTS OF IONIZING RADIATION

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2. Non-stochastic late effects

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1. PURPOSE AND GENERAL VIEW

Late somatic effects of ionizing radiation are either of a non-stochastic or of a stochastic nature. Late non-stochastic radiation damage may occur following accidental (or therapeutically planned) overexposure at high doses. The risk of accidental overexposure is usually considered with regard to workers in nuclear industries. Loss of radioactive sources and, the extremely unlikely event of a large scale nuclear accident could also cause non-stochastic late damage in the general public. Non-stochastic effects occur also as, sometimes inevitable, consequences of radiation therapy of malignant tumours. Although these do not fall, strictly speaking, under the assignments of the Radiation Protection Programme, interchange of information on non-stochastic effects from radiation therapy and from radiation protection has been very valuable.

Stochastic effects, especially malignant tumours could already arise after exposure at low doses, albeit with a small probability. Studies into radiation carcinogenesis span a wide range of approaches ranging from molecular and cellular biology to animal studies and epidemiological follow-ups. Knowledge of the molecular nature of cancer has progressed rapidly during the last few years, in fact more rapidly than during the preceding century, and this will ultimately benefit the understanding of the mechanisms and the prevention of radiation-induced cancer. The results of this programme already indicate such new ways into the future. Investigations into the molecular biology of radiation-induced cancer and into the behaviour of cellular system have expanded considerably. Studies on animals irradiated externally continue to have a certain importance for the elucidation, for example, of the effects of radiation quality, of fractionation and protraction.

The larger part of this sector remains devoted to carcinogenesis from incorporated radionuclides, in particular to the uptake and metabolism of radionuclides and their deposition in relation to target cells for carcinogenesis and non-stochastic effects and the treatment of accidental incorporation. Information from irradiated human population, where available, adds a crucial contribution to the assessment of radiation risks in man.

2. NON-STOCHASTIC LATE EFFECTS

Accidental overexposure leading to late non-stochastic effects most likely affects the haematopoietic immune system, the skin and its underlying tissues, the lens of the eye (which have been treated in the sector "Short-Term Somatic Effects of Ionizing Radiation"), the lung, and the bone. From a point of view of radiation protection, one needs to know which are the threshold doses from which detrimental effects arise following different types of radiation regimens. One has to search for means to recognise the damage at a time when prevention or treatment would be optimal, one must develop adequate forms of treatment and one

must understand factors that give rise to the evolution of late radiation symptoms. These problems can only be solved on the basis of a better knowledge of the pathogenetic mechanisms of late non-stochastic damage. Future work must also attempt to better understand the effects of age, disease and various external and internal factors on the development of late non-stochastic effects as well as the systemic consequences of local radiation damage.

2.1. Mechanisms of action

Late non-stochastic effects assume a great variety of manifestations depending on time after exposure, dose and tissue involved, and underlying concepts to explain them have long been searched for. Damage to the vascular system is thought by many to represent a common denominator for late effects in all tissues, but vascular damage alone cannot explain all the various symptoms observed. A theory on late non-stochastic effects distinguishing two types of response related to the proliferative behaviour of the tissue has recently been proposed and tested (MRC, London, 474) on the epithelium of the oesophagus and on the renal parenchyma. The former would correspond to a cell replacement system (Type H, hierarchal tissue) where changes arrive at a predictable time. Kidney was used as a model for a tissue where functional cells must also be able to provide their replacement (type F or flexible tissue) where the time of appearance is a function of dose and other factors such as additional injury. Among other observations, it was noted that tubular and not vascular damage is probably responsible for renal atrophy since compensation hypertrophy could still be elicited after irradiation.

The role of the vascular system was studied in the central nervous system (see below) and in the hamster cheek pouch (Univ., Oxford, 382), a simple system where blood vessels are only supported by a thin layer of connective tissue. Vascularity (the hit/cut ratio) after doses in the order of 22-25 Gy decreased in a biphasic manner with maxima after 3 and 7 months and with changes in the size distribution of the vessels suggesting loss of capillaries. Increased thymidine labelling was seen for endothelial and, to a smaller degree, for smooth muscle cells.

2.2. The nervous system

Although the adult central nervous system (for the radiosensitivity of the developing brain see Sector "Short-Term Somatic Effects of Ionizing Radiation") is not at risk under conditions usually encountered, it represents a useful model to study mechanisms of parenchymal and vascular damage. It had been mainly chosen because cell division was thought not to intervene in the pathogenesis of late effects in adult brain. Nevertheless, it has now become evident that replacement of glia cells can represent a critical factor in late brain damage.

Late effects in brain were studied following single or fractionated X-ray and neutron exposure (MRC, London, 442). After doses in the order 20 Gy, vascular lesions predominated at late times whereas intermediary damage during the first 3-10 months seemed to be associated with either the neuroglia or with blood vessels. Loss of glia cells in the subendymal plate sometimes leading to necrosis and demyelination of the trigeminal nerve were often seen. Intermediate damage to the spinal cord seems mainly of glial origin. Neuronal damage seemed to be small as judged from measurements of intracellular electric action potentials. Repair in the spinal cord results from a proliferation of glia which divides with a cell cycle of about 1 month compared to much shorter intervals in brain. The percentage of residual injury in the spinal cord (endpoints ataxia and paralysis) increases with the dose and is greater for vascular than for glial damage but is the same for X-rays and neutrons.

Glial damage was also the subject of studies after local exposure to rat brain (CEN-SCK, Mol, 378). Doses of more than 15 Gy completely eliminated beta astrocytes, a newly recognised type of dividing glia cell as shown by its incorporation of thymidine. This effect was more pronounced when the exposure was fractionated. Later when beta astrocytes recover, oligodendroglia became depleted, and a small reduction in macrophages (microglia) was noted.

Vascular damage in the cerebral cortex after local exposure to 20 to 30 Gy was assessed on the basis of vascular density, blood volume index, vessel wall surface and diameter (Univ., Oxford, 490). There was a selective loss of small (<8μ) vessels from 10 to 26 weeks after exposure. Following a temporary return to normal, the number of larger vessels was reduced, perhaps as a compensatory mechanism. These alterations differed somewhat dependent on the cortical zone studied.

2.3. The lung

The lung may be affected by inhaled radionuclides and also represents a critical tissue in radiation therapy of the thorax. Radiation pneumonitis arises a few weeks to months after exposure to 10 Gy and more and is probably related to damage to pneumocytes although macrophages, vascular permeability etc also may intervene. Lung fibrosis develops many months after exposure and is a particularly important and disabling consequence. The mechanisms by which radiation-induced lung fibrosis arises are still disputed. This is regrettable, since lung fibrosis is an important hazard also from other agents in the human environment which may act in conjunction with radiation.

After thorax irradiation, a temporary increase in surfactant, synthetised by pneumocytes II, is observed followed by a late reduction (MRC, London, 474). Since the neutron RBE is about 1 for changes in surfactant and 1.3 for pulmonary death, surfactant changes are probably not decisive for radiation pneumonitis. Leakage of proteins into the alveolar space occurred during early times and again at 15-20 weeks; an increase in leakage into the septal space was seen only during the period of radiation pneumonitis after 3-5 months. The early changes during the first

month may be related to later fibrosis as suggested by concomitant modifications in collagen metabolism. If, indeed, fibrosis depended on vascular leakage and not on clonogenic survival of cells it might be more amenable to therapy.

Morphometric studies on the ultrastructure of the lung after 10-50 Gy exposure to the right lung (CEN-SCK, Mol, 378) indicate that the air/blood barrier increases with time and dose due to an enlargement of pneumocyte type-2 cells and to oedema of the basement membrane. Both, capillary and alveolar, surfaces diminish but the former more strongly than the latter. Attention should also be drawn to the role of alveolar macrophages, particularly when radioactive particles had been inhaled.

Pulmonary alveolar macrophages (PAM) play an important role in removal of foreign particles and defense mechanisms in health and disease. After inhalation by rats of plutonium dioxide in doses capable of causing lung fibrosis, PAM isolated by postmortem lavage display a marked temporary depression in number starting from day 5 (UKAEA, Harwell, 448, 568). Mice appear more sensitive than rats and in SAS/4 mice the acute depression is followed by a chronic depletion with no signs of recovery after 100 days. PAM in another strain of mice recover, however. As fibrosis develops, foamy cells, probably related to macrophages, appear. During PAM reduction, cells are found with micronuclei and multiple nuclei. PAM seem to be composed of two populations with life spans of 7 and 34 days and possibly different radiosensitivities. Probably only one of these populations has phagocytotic activity. After exposure of mice to 930 Bq of inhaled Pu-239 dioxide, signs of fibrosis (increased weight of lung) appeared after 3 months; later fibrosis and increased collagen were noted. Americium produced a smaller effect with an earlier peak than plutonium, probably as a result of the more rapid removal from lung of this nuclide.

3. RADIATION CARCINOGENESIS

3.1. Molecular-biological studies

Most, if not all, tumours are descended from one single ancestor cell which at some time had undergone events transforming it in such a way that it could divide indefinitely, become "immortalised" and escape the control of the organism. Other event(s) which "promote" a single cell or an already preformed microtumour also have to occur before the transformation becomes permanent, and the tumour can grow beyond a critical mass. The transforming event appears to be due to an activation of proto-oncogenes which can occur by several mechanisms, such as mutational damage to DNA, rearrangements of the chromosomal material, uncontrolled amplification of the gene and integration of a retrovirus. Many oncogenes have now been defined, and one has begun to understand how their gene product could alter cellular functions. Several experienced European laboratories

work in this rapidly expanding field, and this subject has been developed in the present Radiation Protection Programme. In view of the new and different approaches used in these studies, it should be helpful to introduce them by a schematic overview:

A) Activation of proviral sequences.
Mammary carcinoma
LTR (long terminal repeat) of mammary tumour virus activated in radiation-induced lobular hypertrophy but not in mammary carcinoma
Leukaemia
Studies on activated murine leukaemia virus recombinants. Interaction of non-leukaemogenic virus with non- leukaemogenic radiation lead to recombinant virus and leukaemia.
Osteosarcoma
Activation of virus dependent on dose, mouse strain and bone tissue development. Studies on new integration sites and molecular structure of the mo virus.

B) Involvement of oncogens.
Mammary carcinoma
No expression of 8 known oncogenes while a new (tno) oncogene was detected in carcinomas.
Leukaemia
Possible integration of RadLV virus near oncogenes in virus-induced leukaemia.
Osteosarcoma
Overexpression of certain oncogenes in several tumours. Detection of certain oncogenes with altered structure at the RNA and DNA level.

The possible role of murine mammary tumour retroviruses in radiation-induced mammary tumours was studied by different methods (TNO, Rijswijk, 376). It was thought that the carcinogenic action of such viruses was mediated by certain proviral sequences, the so-called long terminal repeat (LTR). Although normal rat DNA was found to contain sequences which hybridised with mammary tumour viruses, no transcripts of LTR could be found in 25 rat mammary carcinomas studied (of the tubulo-papillary- or cribriform comedo-type). Such LTR transcripts were, however, detected in radiation-induced lobular hyperplasia or in developing or lactating mammary glands, suggesting their participation in the genesis of the most frequent radiation-induced mammary tumours in the rat. None of 8 different retroviral oncogenes tested were found to be expressed in radiation-induced mammary or pulmonary tumours but about 25% of the mammary tumours contained transcripts of an oncogen capable of transforming NIH/T3 cells. The tno oncogene which is unrelated to any of the known oncogenes was isolated and found to be able to transform murine fibroblasts. The transformation efficiency was greatly enhanced when single strand breaks were present in the DNA or proviral LTR or Moloney leukemia virus were added.

The role of the RadLV retrovirus in radiation-induced murine leukaemia was studied in close cooperation by two laboratories (CEN-SCK, Mol, 379); (Fond. Bergonié, Bordeaux, 371). Upon introduction into a cell, these viruses give rise readily to different recombinants. Apparently, neither appearance of a recombinant nor expression of a complete proviral genome are prerequisites for the malignant state.

This conclusion is based on studies with RadLV leukaemia virus in irradiated C57BL/Ka mice (CEN-SCK, Mol, 379). A gene (env) and the long terminal repeat (LTR) sequences of this virus, the most likely candidates for the thymotropic and leukaemogenic properties, were cloned in a bacterial plasmid. The LTR sequence suggests that these properties may be mediated by an enhancement of an oncogene via neighbouring (not adjacent) provirus insertion. Cells from RadLV-induced thymic lymphomas possess different proviral integration sites but upon culturing, cell lines emerge with all having the same insertion site and apparently overgrown cells having other integration sites.

Three B-tropic retroviruses were characterised as recombinants of N and X endogeneous viruses (Fond. Bergonié, Bordeaux, 371) and produced late B-cell leukaemia, probably as a consequence of secondary genetic recombination (but not thymic lymphosarcoma or T cell leukaemia). Viral recombinants frequently appear in irradiated mice due to an activation of endogeneous viruses. When injection of a virus, not leukaemogenic for T cells, was combined at different intervals of time with a dose which does not induce a significant leukaemogenic response, leukaemia developed suggesting that B-tropic recombinants may act as promoters for thymic radioleukaemogenesis. In this case, leukaemia is prevented by a bone marrow restoration whereas it would not be affected if the leukaemia were of viral origin.

Another set of investigations: (CEN-SCK, Mol, 492; GSF, Neuherberg, 366; Univ., Aarhus, 547) dealt with osteosarcoma. Osteosarcomagenesis by internal emitters leads to activation of endogenous retroviruses which might influence expression of cellular oncogenes and conversely, murine osteosarcoma can be induced by certain retroviruses. These factors and the particular knowledge already acquired in radiation-induced osteosarcoma make this a particularly valuable study.

Activation of proviral genes increases with dose and depends on the mouse strain (GSF, Neuherberg, 366); it occurs earlier and most intensively in those strains with a short latency period for osteosarcoma. Some viruses which were isolated late during the latency period and therefore had a greater chance for modifications in their genome (LTR and envelope region) also exhibit other properties (induction of lymphomas, osteomas and osteopetrosis). The activation of proviruses is followed by an increase in antibodies and by the appearance of free or immune complex-bound viral glycoproteins. Expression of bas-oncogene was increased and altered in certain tumours, and fos or abl-oncogenes were also found expressed in some tumours.

Tumour-bearing mice developed antibodies against viral oncogene-transformed cells.

The FBR murine osteosarcoma virus complex originally isolated from a Sr-90 induced tumour could be separated into 2 components (CEN-SCK, Mol, 492), one being a replication competent leukaemia virus (FBR-MuLV) and the other a replication defective leukaemia virus (FBR MuSV sarcoma virus) which was capable of transforming cells and of encoding an oncogen homologous to the v-fos oncogene. A part of the provirus corresponding to the oncogene has been cloned and is analysed for its nucleotide sequence. Several retroviruses that had been expressed in Sr-90 induced osteosarcoma of CF1 mice were characterised. They caused lymphomas in new-born mice but did not induce osteosarcoma. The pattern of integration of proviruses in 8 different osteosarcomas differed, and no common restriction fragments could be detected. Retroviruses inserted in the genome might influence expression of oncogenes but no elevated expression of different oncogene messenger RNA transcripts could be observed in osteosarcoma cell lines from radiogenic tumours. A ras related oncogene was, however, found expressed in form of a 25 000 dalton protein in 3 out of 16 cell lines.

Additional molecular studies (Univ., Aarhus, 547) support these findings on retroviruses. The complete nucleotide sequence of 8,371 of the Adv murine RNA genome was determined. Selected regions of an osteosarcoma virus, in particular the LTR sequence, were also analysed, and certain regions have been cloned to provide a highly sensitive tool to characterise the proviral structure, its integration site and the amount and structure of viral RNA in tumour cells.

3.2. Cellular studies

During recent years, assay systems have been developed which allow the detection of transformation in cultured cells. The advantage of these procedures is evident: transformation can be readily assessed on the basis of changed growth characteristics, dose-effect relationships can be obtained down to very low doses and the influence of radiation quality can be investigated. Experiments on the effects of protraction, fractionation and promoting factors are also feasible to a certain extent. The disadvantages are: the transforming event in vitro may be unrelated to the appearance of a tumour in vivo and the outcome depends on culture conditions; density of cells etc. Moreover, most tests so far have been performed on cells of mesenchymal origin, but systems using epithelial cells are now also rapidly being developed. European research had lacked behind in this subject for some time, but during the latter part of the past, and even more in the new 1985-89 programme, has been gaining momentum.

Immortalisation of cells, i.e. the capability to undergo an unlimited number of cell divisions in contrast to the limited life span of normal somatic cells, is related to malignant

transformation. The lifespan of cells was determined by carrying out subcultures until extinction of the cell line (Assoc. CP. Bernard, Paris, 352). The lifespan was shortened by 1 Gy of low dose rate (2.8 mGy/min) exposure. Shortening was more pronounced in adult than in embryonic lung fibroblasts. There were more chromosomal aberrations in non-irradiated adult than in embryonic cells but only those in the former increased after irradiation, suggesting that cells with a high potential for chromosomal rearrangements survive better. Cells from donors with high cancer risks had an increased life span after irradiation indicating a predisposal for transformation. The extinction of a cell line and the increased radiosensitivity in aged cells is thought to result from a reorganisation of the genome and from somatic mutations. Circular DNA, altered chromatin fibres and reduced hybridisation with alpha-actin and beta-globin gene probes could be detected in such aged cells.

Transformation frequencies and survival have been determined in C3H10T1/2 cells irradiated with 31 MeV protons (Univ., Milan, 552). The ratios transformed to surviving cells were found to be constant in the dose range 0.25 to 1 Gy and equal to about 8 times the spontaneous rate. At higher doses, they increased with dose to about 250 times (at 7 Gy) of the spontaneous rate.

Several other studies on cell transformation are mentioned in other sectors of the programme.

Transformation, together with chromosome aberrations and survival were studied after exposure of C310T1/2 cells to X-rays and 0.5, 4 and 15 MeV neutrons (TNO, Rijswijk, 300). Frequency of transformation is only 1/1,000 of that of reproductive death and the maximum RBE values i.e. the ratios of the linear parameters of the linear-quadratic dose response relationship are about the same as for reproductive death.

Thyroid cells in culture were studied for radiation-induced transformation (Trinity College, Dublin, 364). Immortalisation (viability of subcultures), growth in soft agar (anchorage independence), loss of contact inhibition and altered LDH isoenzyme pattern were found following irradiation. A dose effect curve for growth in soft agar shows a peak at 5 Gy.

No transformation could be achieved in fibroblasts of patients with xeroderma pigmentosum, therefore transformation of NIH 3T3 cells was used for detecting oncogens (Univ., Rotterdam, 404). Various cell lines with abnormal repair were immortalised with SV 40 virus (Univ., Sussex, 414). Levels of cycline, a nuclear non-histone protein, are elevated in dividing compared to non-dividing cells and this was also observed in transformed cells (Univ., Aarhus, 416). Fibronectin secretion was found to be normal in X-ray transformed fibroblasts and reduced in spontaneously transformed ones suggesting a qualitative difference between spontaneous and radiation-induced transformation (ULB, Brussels, 359). Fusion experiments indicate that transformation behaves as a recessive trait, and that

changes in chromsome number also may play a critical role in transformation. Cells transformed by the Simian SV40 virus were used to study repair (Univ., Leiden, 405). An attempt to develop a transformation system with BHK21 C13 Syrian hamster fibroblasts (UKAEA, Harwell, 305) a system attractive because it allows concomitant determination of locus mutations (hypoxanthine phosphoribosyl transferase) so far has not given reproducible results after radiation.

3.3. Radiation carcinogenesis after external irradiation

Many studies in the past have dealt with the carcinogenic effects of external radiation, and it has become clear that incidence as well as type of cancers not only depend on dose and exposure conditions but also on species and strain of the experimental animal. Consequently, such studies have become much more selective, searching for specific types of cancer relevant to the human situation or studying the influence of fractionation and radiation quality for which quantitative or semi-quantitative extrapolations appear feasible. The question of the quality factor of neutrons was the theme of a symposium on "Neutron Carcinogenesis" held together with the TNO at Rijswijk, March 1982. (Annex V).

A unique population of rhesus monkeys which had been exposed to X or neutron irradiation and for which age-related controls are available is followed (TNO, Rijswijk, 567) in a life span study for tumour induction and other late effects. The monkeys have now arrived at 2/3 of their expected life span, including 85 monkey years with a mean neutron dose of 3.4 Gy and of 219 monkey years with a mean X-ray dose of 7.2 Gy. Significantly more bone, kidney, thyroid, CNS and glomus tumours were observed in the irradiated monkeys and a preliminary estimate of the RBE yielded a value of 4 or 8 dependent on the mode of calculation.

A life time study on rabbits exposed to gamma doses from 1-11 Gy has been continued but is not yet terminated (duration about 9 years) (MRC, Chilton, 385). Among the notable findings are increased incidences of basal cell carcinoma in skin, Sertoli cell tumour in testis, fibrosarcoma and osteosarcoma.

The influence of fractionation and radiation quality of D(50)-Be neutrons on tumour incidence and disease spectrum was investigated in more than 10,000 mice from two strains of different tumour spectra (CEN-SCK, Mol, 378). After gamma irradiation, one strain, BALB/c, exhibited a linear dependence of survival on dose, the other (C57Bl) a sigmoid one. Fractionation increased the incidence of tumours. For BALB/c mice the RBE of these neutrons did not differ from 1, and the disease spectrum was similar. In C57Bl mice, the survival-dose dependence was linear for neutrons (due to non-stochastic lung and kidney diseases) and the RBE depended on dose but was generally slightly higher than 1. Fractionation of neutrons did not have a great influence on the animals studied so far.

Survival and different tumours were studied in X-ray and fission neutron irradiated mice of different ages (ENEA, Casaccia, 298). Young adult mice were found to be particularly sensitive to tumour induction by neutrons, and ovary and liver tumours were determined in prenatally irradiated mice. A large experiment studying ovarian tumours after irradiation with monoenergetic neutrons has also been initiated. The evaluation of all these data is still under way.

Mammary tumours in the rat are used to verify the validity of extrapolation to low doses and different radiation quality of human epidemiological data. Incidence of mammary tumours was studied in 3 rat strains with different tumour spectra and sensitivity after X-ray or 0.5 MeV neutron irradiation (TNO, Rijswijk, 375). Excess of mammary carcinoma in WAG/Rij rats depended linearily on dose for both X-rays and 0.5 MeV neutrons. The RBE was about 15, irrespective of the radiation dose. When neutron or X irradiation was fractionated, about the same number of tumours appeared at the same age as after single exposure. This could result from a larger efficiency of tumour formation after fractionation or from a greater susceptibility of older animals. In consequence, the rat model would support a linear extrapolation of epidemiological data to low doses.

Radiation-induced skin tumours arise usually on damaged skin. Initially mice were exposed locally to their skin with a beta dose giving submaximal tumour incidence, and this was followed 3 or 12 months later by an immunosuppressive whole-body dose (5 Gy) (MRC, Chilton, 385). This latter exposure damages epidermal dendritic Langerhans cells which may be involved in immunological surveillance. The data which are not yet complete should give information on immunological factors in skin carcinogenesis.

Synergism between exposure to radiation and a chemical agent (N-nitroso-N-ethylurea ENU) immediately after birth was studied with respect to formation of glioma and schwanmoma tumours in the nervous system (MRC, Chilton, 385). ENU as well as radiation alone can cause neurogenic tumours but ENU followed by radiation resulted in a lower tumour incidence as expected perhaps because irradiation eliminated transformed cells. Application in the inverse order did not have this effect.

A pilot study assessed the value of goitrogen (aminotriazol) treated rats as a model for radiation-induced thyroid cancer (Univ., Cardiff, 569). Irradiation alone did not cause any tumours after 4 months and very few after 8 months. When the thyroid was stimulated with aminotriazol a significantly increased incidence of independence of radiation dose was observed, particularly when treatment started 10 days after irradiation. In the next phase of this experiment, a larger number of animals will be employed, and it should become possible to assess the carcinogenic effect in thyroid of as little as 10 m Gy.

Another study dealing with the carcinogenicity of I-123, I-124 and I-131 on mouse thyroid had essentially negative results, and no thyroid carcinoma could be observed (TNO, Rijswijk, 374).

4. METABOLISM OF RADIONUCLIDES

4.1. Intestinal Absorption

Absorption from the gastrointestinal tract is a main route of entrance of radionuclides into the body of the general public. ICRP has defined values for the purpose of calculating limits of intake mainly for workers. For the general public these values are not always relevant. Radionuclides, particularly when they have passed a food chain, may change their physicochemical, chemical or metabolic characteristics, and food composition, age and disease also can affect intestinal uptake. Finally, the dose and possible damage to the intestine from poorly absorbed radionuclides have been inexactly estimated since adherence to the surface of the intestine has been neglected. These factors are now being studied in more detail and will still require attention in the future.

Absorption of Np, Pu, Am and Cm from the gut of rats and rabbits has been studied, dependent on animal age and chemical forms (NRPB, Chilton, 388), and values for absorption relevant to the general public have been proposed. For the adult these are mostly identical to those ICRP has suggested for workers. For neptunium, the current ICRP value (1%) appears too high since it had been obtained with amounts causing damage to the intestine. Complexing plutonium with phytate and citrate or incorporating it into liver increases absorption in hamsters by a factor of 2 to 5 whereas americium behaves in the inverse way. For children (from birth to one year) it is suggested using an absorption coefficient 10 times, and for infants fed only on milk 20 times greater than that of adults. Dose calculations to the intestine from retention to the intestinal wall yields much higher local doses than thought before, but this would affect significantly committed doses to the total organism only for the short lived Cm.

Intestinal absorption of neptunium was also studied in monkeys (CEA, Fontenay-aux-Roses, 565) since some reports suggested that this element could be a critical risk from the nuclear fuel cycle. With amounts relevant to radiation protection, absorption of four-valent Np is about 0.01%, i.e. 10% of the current ICRP value and is influenced by the dietary regimen to a certain extent: large amounts of food containing acids and alcohols, for example fruits, enhance intestinal absorption but also increase subsequent urinary excretion. A diet rich in milk reduces Np absorption whereas one rich on phytates (potatoes) increases absorption and retention by a factor of 3. A previous 24 hour starvation period increases absorption by a factor of 10. The five-valent Np is better absorbed as shown by experiments where large amounts of ferric ion had also been fed.

4.2. Behaviour of inhaled radionuclides and lung models

Inhalation is a principal route of entry for many harmful agents including radionuclides. In contrast to the relevant short transit in intestine, residence in lung can be long, dependent on the site of deposition and on chemical and physical properties of the inhaled material. Moreover, lung is a complex tissue in which the target cells for lung tumours are present only at certain anatomical sites and are still poorly defined. Lung models for deposition and clearance of radioactive particles and gases are available but recent results indicate the need for improvement. These points were considered in a workshop on "Lung Models for Inhalation of Radioactive Materials" organised together with the NRPB at Oxford, March 1984. See Annex V. Questions requiring particular consideration are: behaviour and dose of radioactive aerosols in nasal passages, long-term behaviour in bronchi and bronchioli, determination of parameters for lung models in man and the influence of different factors (disease, smoking), characteristics in the lung of radioactive industrial dusts, determination of radioactive lung burden in vivo, microdosimetry of target cells.

The lung model proposed by ICRP is unsatisfactory with respect to deposition and clearance of material deposited in nasal passages and the tracheobronchial tree (NRPB, Chilton, 489) and does not allow reliable calculation of exposure to these structures. Studies to determine deposition of aerosol of different sizes from 0.1 μm up to the size that can penetrate into the nasal vestibule under controlled conditions at different rates of breathing are now under way and a dosimetric model to determine doses to stem cells of the nasal and tracheobronchial epithelium has been developed.

A lung model to determine the dose from radon daughters has also been improved taking into account the thickness of the mucoscal layer and the site of the potential target cells (Polytechnic, London, 544).

Although the overall retention pattern has been studied frequently, the fate of individual particles deposited in different lung structure remains uncertain with respect to the mechanism of transport from alveoli to lymphatic drainage and peribronchial retention sites (MRC, Chilton, 384). Particles introduced in subpleural alveoli by micropipettes are taken up rapidly by macrophages within 5 hours, but not in any other cells, and there was no mucociliary clearance towards the stomach. Some macrophages with particles were seen at the luminal surface of terminal broncheoli and also at the alveolar side of the walls of alveoli and blood vessels.

The behaviour in man of relatively insoluble (class Y) particles remains still uncertain (NRPB, Chilton, 489). Human volunteers were followed up to 18 months after inhalation of 1 or 4 μm particles. Tracheobronchial clearance was in the order of 6 days but no indication could be found for the rapid clearance phase

(less than 1 day) postulated by the ICRP model. Long term retention was in the order of 50% and much dependent on individual characteristics. Parallel investigations on rats and hamsters show that mechanical tracheobronchial clearance depends on the species but is independent of the material unless activities are so high as to affect physiological mechanisms. On the other hand, translocation of material from lung to blood is not very dependent on species.

An attempt was made to define those areas in human lung where insoluble particles are retained for long periods of time (MRC, Chilton, 384). Uranium which could have been detected by neutron-induced autoradiography was not found in lung sections from persons working in tin mines and which had been exposed to dusts for long periods of time. Boron dust from tourmalin yielded, however, a suitable marker by means of the $^{10}B(n,alpha)^{7}Li$ reaction and is being followed in comparative studies in man and rats.

Most inhalation experiments are carried out with standardised actinide aerosols. Actual dusts at the work place or in the environment contain extraneous material of different physicochemical characteristics and/or a mixture of radionuclides. The influence of firing temperature on the solublity of PuO_2 was determined in mouse lung (UKAEA, Harwell, 386). Retention of Pu-239 appeared to be independent of firing temperature and could be described by a 2 component exponential sum. For Pu-238, initial rates of clearance were smaller probably due to its greater toxicity. At later times, the Pu-238 fired at a higher temperature was metabolised more rapidly, the difference probably being due to radiolytic decomposition of Pu-238 of high specific activity.

Since long term retention in lung is largely determined by solubility characteristics, a device of "mock lungs" has been developed to determine long-term solubility characteristics under sham physiological conditions (UKAEA, Winfrith, 380). Considerable effort has been made to approach such conditions and material obtained from ball milling of nuclear fuels is now being assayed. Although the experiments are not yet complete, marked differences have already been noted in transfer between uranium, americium and plutonium.

Image analysis of alpha tracks from Pu-239 particles deposited in lung alveoli from rat, dog or man (Polytechnic, London, 381) yielded histograms of dose distribution as a function of distance, the volume of tissue receiving a particular specific energy and the energy deposition in alveolar cells and their nuclei. Energy depositions in targets can vary over several orders of magnitude, much more than has been predicted by simpler models, and the biological implications of this are now investigated. Pulmonary distribution of alpha emitters, including Po-210, is also studied in humans (smokers and non-smokers) (Univ., Bristol, 564), and these investigations are

now extended to material obtained from persons living near the Sellafield nuclear plant.

4.3. Behaviour of radionuclides inside the body

Transport of actinides mobilised in lung depends on chemistry and size of the inhaled aerosols (NRPB, Chilton, 388). Small plutonium particles inhaled as such or produced by radiolytic degradation of larger ones are transported unchanged and are preferentially excreted during the first phase of lung clearance. Subsequently, reaction of Pu-238 with phospholipids of lung surfactant and/or entrainment within macrophages dominate. The latter material being probably in monomeric form can be readily removed by aerosols or intravenous injection or acetic acid. These treatments are still effective when started 2 weeks after contamination. On the other hand, inhaled Pu-tributylphosphate is transported as negatively charged colloids. Injections of diethylenetriaminopenta acetic acid (DTPA) are also effective in this case probably because they inhibit polymerisation of Pu in lung and the binding of the colloid to serum proteins. Treatment of americium contamination requires longer treatment due to the slower formation of transportable material. Studies on inhaled uranium compounds indicate that it is translocated as carbonate complex.

Transferrin, the protein transporting iron in plasma, also reacts with plutonium in the form of citrate, nitrate, tributyl phosphate or nitrilotriacetate since iron and plutonium ions resemble each other (KfK, Karlsruhe, 367). Plutonium binding to Licam(C) was found to be 2-5 times more effective than DTPA for removing plutonium from transferrin although the relative binding constants would suggest a much greater difference. Transferrin receptors appear not to play a role in the uptake of Pu by cells and binding to transferrin reacts with Pu citrate and nitrate and tributylphosphate in blood in a similar way as with Fe.

Contamination and behaviour of uranium were studied in an industrial plant using uranium tetrafluoride (CEA, Pierrelatte, 372). Studies in vitro indicate that this material is converted to oxide and hydroxide, and that, consequently, its removal occurs more slowly than specified by the ICRP model. This has also been confirmed by studies on rabbits. Determination of uranium in urine is insufficient to evaluate the uranium body burden, and determination of fecal uranium is needed.

4.4. Decorporation of incorporated radionuclides

Despite several new developments, the use of the chelating agent DTPA in form of its different salts remains the proven method for removal of incorporated heavy metal radionuclides, in particular of actinides. There are certain limitations with respect to DTPA treatment. It must be started shortly after contamination (although some recent data indicate that it can be also effective at a later time) and DTPA is rapidly excreted so that maintenance of a therapeutically effective dose requires repeated

applications. One must also learn to avoid a depletion of essential elements from the body if DTPA is given for longer periods of time. Considerable progress has, however, been made in treating accidental incorporation from ingestion, inhalation or through wounds, and future efforts can be directed to recommendations on how a given situation should be handled. It should be added that this progress would not have been possible without a better understanding of the mechanisms of transport and binding of radionuclides in the body. In addition, to DTPA three other compounds have been investigated. None of those seems to be the panacea for decorporation but they may have well defined applications.

Prompt treatment by repeated inhalation or intravenous injection of Zn DTPA can reduce lung deposits of Pu-238 nitrate to about 1 % and extrapulmonary Pu to about 50 % (NRPB, Chilton, 388). Larger masses of plutonium lung deposits are not as easily accessible; nevertheless weekly treatment with ZnPTA diminished lung content to about 10 %. Intraperitoneal injection of ZnPTA was also effective against Am contamination. Actinides deposited outside the lung are however not very accessible. Pu-tributylphophate (Pu-TBP), a compound used in the Purex process of the nuclear fuel cycle, also could be removed by prompt DTPA treatment, but extrapulmonary deposits required protracted treatment. The reason for the failure to remove Pu-TBP in the CEA studies probably is the greater mass of contaminant employed in the latter studies.

Decorporation of a radionuclide or its movement to other sites may not imply a reduced risk (CEN-SCK, Mol, 377). Therefore, decorporation of radium and americium from bone was studied to discover whether it brings about a reduction in toxic effects. The number of haemopoietic stem cells, particularly those forming spleen colonies (CFU-S), in bone marrow was initially reduced after injection but often recovered later. Damage depended on the bone structure and the radionuclide studied; it was greater in bones with large internal bone surfaces than in the femur (although calculated doses did not differ much) and for the surface seeker Am than for the volume seeker Ra. Decorporation with ZnDTPA did not necessarily reduce damage to the same degree as it removed radioactivity.

Attempts have also been made to give ZnDTPA orally (KfK, Karlsruhe, 367). This treatment was remarkably effective in removing Pu or Am 4 and 30 days after contamination. However, intravenous treatment is still recommended immediately after contamination. A chelating compound (Puchel) which enters cells and which had been developed in the earlier programme was confirmed to be no more effective than ZnDTPA but much more toxic and is therefore not recommended.

DTPA is not very effective for decorporation of radioactive alkaline earths. A compound tailored to the shape of such ions is cryptate-222 (GSF, Neuherberg, 365). It removes barium almost completely from extra-cellular space if given immediately after

exposure and at a sufficient dosage might also be used in case of Ra or Sr provided its toxicity could be reduced. At later times, cryptate does not seem to be useful. An insoluble boron arylic cryptate was developed to stop intestinal absorption and substantially lowered uptake of strontium if given within 10 minutes after contamination.

The metabolism of Pu-TBP has also been studied in monkeys after inhalation (CEA, Fontenay-aux-Roses, 370). It is cleared from lung with a half life in the order of 100 days and transferred mainly to liver and later to bone. There are differences in behaviour between rats and monkeys, and the ICRP model does not describe well the behaviour of Pu-TBP. Decorporation by DTPA is not very effective and requires repeated administration of relatively high amounts of Ca or Zn DTPA. Shortly after inhalation, lung lavage seems to be most useful, and 5 washings remove in the order of 60 % of Pu-TBP inhaled.

Licam(C) a new compound prepared in the US seems to be promising for removing plutonium on the basis of its in vitro properties. In order to speed up therapeutic application of this drug, the Radiation Protection Programme had this compound synthetised (CEA, Fontenay- aux-Roses, 558). It was then tested according a protocol elaborated by EULEP (CEA, Fontenay-aux-Roses, 370; CEN-SCK, Mol, 377; KfK, Karlsruhe, 367; NRPB, Chilton, 388). Several animal species, including monkeys, and several modes of application, including inhalation, were used. Licam(C) was found to be very effective - more than DTPA - in reducing bone retention of plutonium but not of americium. Accumulation of plutonium in the kidney limits however the therapeutic usefulness of Licam. There still remain questions as to the purity of the Licam used.

5. HARMFUL CONSEQUENCES OF INCORPORATED RADIONUCLIDES

Work on the harmful effects of incorporated radionuclides concentrated on lung, bone (and liver). These priorities were chosen because lung is not only a principal site of entry and deposition of inhaled radionuclides but also the tissue in which radiation-induced cancer (from natural radon and its daughters) represents the most important risks to man. Many long-lived radionuclides are deposited in bone, and the most extensive data on human cancer from incorporated radionuclide are available for osteosarcoma after incorporation of radium. Distribution of radionuclides in the tissues as well as distribution of target cells for carcinogenesis is very inhomogeneous. Definition of target cells, of their life cycle, migration, radiation response, and their localisation with respect to deposited radioactivity represent therefore major problems for assessing risks from incorporated radionuclides. Several factors (age, disease, animal species and strain as well as on the time course of irradiation) must be considered in this respect, and all of this makes it difficult to extrapolate animal experiments to the human situation.

5.1. The lung

The extensive data obtained on lung cancer in rats following radon inhalation by the CEA were evaluated (Univ., Würzburg, 461) by newly developed statistical tests. All dose groups were jointly analysed in terms of the proportional hazards model, the accelerated time model and the shifted time model. Data agreed best with the accelerated time model. Comparison with neutron data indicated that the time dependency is similar and that correspondingly 3 WLM of radon correspond to 1 mGy of neutrons.

Studies to expose rats to radon under well-defined conditions were also initiated (TNO, Rijswijk, 301). Exposure facilities were constructed, and conditions allowing long-term exposure were optimised. Exposure has now been started. Moreover, a dosimetric lung model had to be adapted on the basis of histological sections from rat lung.

Mice were exposed to Am-241 aerosols to an initial lung burden of 0.5-226 Bq, and lung tumours were scored after 1 year (St Barth. Hosp., London, 383). Lung removal and accumulation in bone is more rapid than observed earlier for Pu-239. When repeated inhalations were given to match the dose of Pu-239 about the same number of tumours was observed as in the earlier study but a direct comparison is difficult because another mouse strain had to be used. In another experimental series, mice were repeatedly exposed to Pu-239 aerosols in such a way as to maintain an approximately constant lung burden. When compared to earlier data with a single inhalation it appears that only the first inhalation had been effective in causing lung tumours but the data are not yet fully evaluated.

A pilot experiment was started to assess the possible synergistic effects between tobacco smoke on plutonium-induced lung cancer in mice (UKAEA, Harwell, 568). Exposure facilities were set up and deposition of tar was determined.

5.2. Osteosarcoma from internal emitters

Osteosarcoma is a principal risk from bone-seeking radionuclides. Epidemiological data are available for long-lived and short-lived radium isotopes but extrapolation to actinides requires confirmation by animal experiments.

The dependence of osteosarcomas in mice on spatial and temporal distribution of dose was studied using different bone seeking beta and alpha-emitters (GSF, Neuherberg, 366). As lower doses of protracted Lu-177 beta radiation (skeletal dose 8 Gy) were given the difference to single application disappeared (risk 6 x 10^{-3}/Gy in NMRI mice) but the efficiency per Gy was lower than for higher protracted doses. Continuous alpha irradiation had the same efficiency as a discontinuous fractionated one indicating that no repair had intervened. In conclusion, a) multiple application of short-lived radionuclides may be as hazardous, or more so, than that of a long-lived one, b) at low

doses osteosarcomogenesis decreases, and differences between protracted and single application disappear. Several factors influence osteosarcoma incidence. Beta emitters have a higher osteosarcomgenetic potential in one year old than in new-born mice. Strain disposition is probably related to metabolic features and susceptibility to activation of proviral genes. Many other factors tested were found to have no effect on risks of radiation-induced osteosarcoma, ie substances stimulating bone resorption (cadmium chloride), inhibiting bone resorption (indomethacin) or causing exostoses (beta-aminopropionitrile), inhibiting T-suppressor cells (cyclophosphamide), having cytostatic potential (daunomycine), or activating the genomes of retroviruses (5-azacytidine).

Cultured stromal cells (CFU-f) from bone marrow of perinatal, young and adult mice were studied in culture after exposure of the animals to different doses of Am-241 (CEN-SCK, Mol, 566). These fibroblasts which may be related to the target cells for osteosarcoma induction were found to be radiosensitive and thus must be situated in the range of the alpha rays of Am.

A large group of mice had been injected with Pu-239 at (ENEA, Casaccia, 323). Doses ranged from 1.2 to 120 nCi/kg body weight, and survival as well as histopathology is being assessed. The data so far do not show any effect of plutonium at levels up to 300 pCi/mouse (i.e. an average skeletal dose of 0.1 Gy).

In another study (Univ., Bristol, 564) mentioned elsewhere, microdistribution of Ra-226 and Ra-224 was studied in cooperation with the MRC, the KfK and the University of Utah allowing eventually similar investigations in man.

6. EPIDEMIOLOGY

Epidemiological data, where available, provide the confirmation for the assessment of radiation risks to man (see sector "Evaluation of Radiation Risks"), they require however meticulous planning, consistent execution and careful evaluation. There exist only few populations for which the dose has been sufficiently high that one can expect significant results and for which suitable controls are available. The validity of epidemiological studies and the possibility to extrapolate them to other radionuclides and exposure conditions is greatly extended if they are combined with experimental studies comparing the conditions studied in man with those not observable in man. This has been a main feature of the two large epidemiological investigations supported by the Radiation Protection Programme and dealing with cancer and non-stochastic changes, mainly in bone, after application of radium-224 and of cancer and non-stochastic changes in liver after application of thorium dioxide gels (Thorotrast) (DKFZ., Heidelberg, 368). The "Radiobiology of Radium and Thorotrast" has been discussed together with scientists disposing of similar data from the USA

and Japan at a symposium organised with the GSF at Neuherberg, October 1984. (See Annex V).

One project concerned the development of mathematical tools to re-evaluate the epidemiological data from the Japanese survivors of the atomic bomb explosion in cooperation with the Radiation Effect Research Foundation (Univ., Würzburg, 286). Isotonic regression methods based on maximum likelihood procedures and yielding monotonous dependence of prevalence on dose and time were developed, and graphs of mortality from cancer or leukaemia in terms of location have been prepared. These data will greatly facilitate the re-evaluation once the new dose estimates will become available. Attention is also directed to the development of methods to derive limits of uncertainty, and it should be pointed out that several mathematical and statistical problems remain to be solved and that also better semi-empirical methods are needed.

The short-lived radionuclide radium-224 had been given for ankylosing spondylitis as well as for a variety of other diseases. Two groups of persons are distinguished in this context (GSF, Neuherberg, 461). A high dose group consisting of 218 juveniles (average skeletal dose 10.6 Gy) and 681 adults (2.06 Gy) so far has yielded 53 bone sarcoma (but with decreasing rate in recent years), 59 cancers of soft tissue and also an excess of liver and kidney diseases. The most recent and surprising findings are non-stochastic effects, exostoses, growth retardation (2 % of potential growth/Gy), tooth breakage and cataracts. US scientists from Utah and Argonne also cooperate in these studies. The low dose group, a group of 1,501 ankylosing spondylitis patients received radium yielding doses in the order of 0.67 Gy to bone. Three skeletal cancers have so far been observed instead of 5.8 predicted from the high dose group as well as 3 cases of chronic myeloid leukaemia, none of which have so far occurred in the control or in the high exposure groups.

Appropriate methods and modalities as well as computer programmes were developed to estimate the parameters and modes of risks in these epidemiological as well as in the accompanying animal studies (for example, accelerated appearance of tumours, increased total incidence, etc.) (Univ., Würzburg, 461). These methods were applied to the experimental studies on bone cancer from bone seeking radionuclides, on lung cancer from radon and on the RBE of mammary tumours. Part of the latter studies were also carried out in cooperation with Brookhaven National Laboratory, USA.

7. COOPERATION IN LATE EFFECT STUDIES

Late effect studies require a long and expensive commitment in manpower, experimental know-how, exposure facilities and animal care. Careful planning and consistent execution, often over 5 and more years, are indispensable to bring such studies to a successful conclusion. Cooperation among institutions and among

scientists from different places and countries much reduces the risks and costs of such experiments. The Commission has paid much attention to these aspects and provided consistent funding, regular exchange of information by study groups between contractors and has initiated cooperation between different institutions within the Community as well as with countries outside.

In addition, the Commission has initiated and funded the European Late Effect Project Group (EULEP, 390, 491), an association of European scientists encompassing relevant institutions in the Community. EULEP has been effective in creating a climate of personal collaboration and in maintaining a uniform high standard of execution. EULEP also organised, with the concurrence of the Commission, workshops and symposia; the proceedings of several of them have been published. Dosimetric performance in member laboratories is assured by carrying out regular intercomparison programmes, by formulating protocols and codes of practice for biological experiments and by providing technical aid when special dosimetric problems arise. Diagnostic expertise in radiation pathology is provided and diagnosis of late radiation effects is standardised. To this end, regular slide seminars are held, a consultation centre is maintained, and an atlas of radiation pathology is edited which has been favourably acclaimed internationally. Joint experiments are planned and executed by defining common protocols, by short-term exchange of scientists utilising equipment not available in the other laboratory or providing special techniques and by the exchange of material obtained.

EULEP has concentrated its activities on several areas - the number of participating laboratories is given in parenthesis - namely the role of retroviral genes and oncogenes in radiation-induced osteosarcoma and leukaemia (5), the role of vascular damage in the genesis of late damage in adult brain (6), the pathogenesis of pulmonary fibrosis after external and internal irradiation (3), vascular damage in the hamster cheek pouch (3), metabolism, dosimetry and effects of bone seeking radionuclides (6), deposition, clearance and consequences of inhaled radioactive particles, decorporation of incorporated radionuclides (5). The latter group also published a protocol for testing decorporating agents and studied the possible usefulness of Licam(C). Cooperation on prenatal irradiation extended to the radiobiology of cultured embryos (2), late effects in the brain (4) and the effects of prenatal application of radionuclides on thyroid development (3). Details of most of these activities are found elsewhere in this review. An advantage of this collaboration was, however, that it could be possible to make use of the know-how of some laboratories not funded by the Commission.

8. PERSPECTIVES AND RECOMMENDATIONS

Late non-stochastic damage as a consequence of radiation accidents is being better understood due to studies on suitable models. Such studies must continue to be carefully chosen to obtain results valid for determining threshold doses and mechanisms of action.

A few studies on radiation carcinogenesis after external irradiation, including one on monkeys, have been carried out. While large scale animal investigations of this type are expensive, selected studies obtaining information on quality factors, behaviour at low doses and age dependency of induction are still required.

Few studies on cell transformation in vitro have been carried out in the programme; this system, although still limited in its application to risk assessment, is further developed in the 1985-1989 programme.

The recent expansion in the understanding of the role of oncogenes and viruses in cancer has also its impact on radiation biology, particularly with respect to osteosarcoma, leukaemia and breast cancer. Such studies are promising to give a better understanding of radiation-induced cancer and should proceed in line with the general development of this field.

Radionuclide metabolism has been intensively studied in the programme, particularly with respect to absorption and inhalation. The effects of age and physicochemical speciation are being increasingly considered, and this remains an important task for the future. Particular attention should be given to models for inhalation/clearance and intestinal absorption.

The relation between deposition of radionuclides, target cells and biological effects is crucial for the extrapolation between different exposure situations. Although progress has been made, for example with respect to bone cancer, this remains an important task for future work on lung, bone and liver.

Epidemiological studies on radium and thorotrast have given valuable information on risks of bone and liver cancer as well as on non-stochastic changes in man. Relevant populations being rare, any such study which promises valid data should be continued.

SECTOR E

GENETIC EFFECTS OF IONIZING RADIATIONS

1. General purpose and overview

2. Repair of genetic damage in prokaryotes and eukaryotes

   2.1. The conservation of repair genes and enzymes during evolution
   2.2. Induced repair in microorganisms and mammalian cells
   2.3. Transfection of repair genes into repair deficient cells
   2.4. Characteristics of repair deficient cells
   2.5. Repair in yeast cells

3. Genetic effects in somatic cells

   3.1. DNA damage, repair and cytological effects
   3.2. Studies on plants
   3.3. Somatic mutations in mammalian cells
   3.4. Cytogenetics and radiation sensitivity
   3.5. Factors affecting genetic damage in somatic cells, particularly in lymphocytes
   3.6. Application of lymphocytes for biological dosimetry

4. Genetic effects in germ cells

   4.1. Genetic studies on drosophila
   4.2. Genetic studies on mammals
   4.2.1. Radiosensitivity of male germ cells
   4.2.2. Non-disjunction
   4.2.3. Translocations and deletions
   4.2.4. Mutations
   4.2.5 Consequences of germ cell damage

5. Perspectives and recommendations

1. GENERAL PURPOSE AND OVERVIEW

Within the Radiation Protection Programme of the Commission, work has been carried out on the genetic effects of ionizing radiations, concentrating on three main themes:

- Repair of Genetic Damage in Prokaryotes and Eukaryotes
- DNA Damage and Cytogenetic Effects
- Genetic Effects in Plants, Insects and Mammals.

Radiation induced damage to the primary target DNA is eventually responsible for the biological effects such as chromosomal aberrations and mutations encountered in both somatic and germ cells as a consequence of radiation. The repair of DNA damage can reduce the effect of radiation if it restores the original situation, but may increase the effect if it is error-prone repair. Cells deficient in one or more pathways of DNA repair can exhibit an enhanced sensitivity to radiation and an elucidation of the nature of repair deficiencies may lead to the characterisation of critical DNA lesions in normal cells. Patients with DNA repair deficient cells are often prone to cancer and this emphasises the relevance of radiation induced DNA damage in somatic cells to radiation carcinogenesis (see Sector D, Late Somatic Effects of Ionizing Radiation).

The association between DNA damage and cytogenetic effects can also provide information on the nature of critical DNA lesions, and measurements of cytogenetic effects can be used to estimate exposure levels or to develop techniques of extrapolating data measured in animals to provide risk estimates for man.

DNA damage in germ cells may be transmitted to following generations as dominant and recessive mutations. Measurements of radiation induced genetic effects using different repair proficient and repair deficient organisms may provide an understanding of the mechanisms involved and contribute to an estimation of the genetic risk for man.

Although much of the research carried out in the Genetics Sector is of a basic nature, the programme has not lost sight of the fact that it must provide results directly applicable to radiation protection. This is evidenced by the following examples of important results obtained each time by a group of collaborating institutes.

- A series of contracts have shown that unrepaired and misrepaired DNA double strand breaks are responsible for cell reproductive death in yeast cells; that DNA double strand breaks are the most important lesion leading to the formation of chromosome aberrations in mammalian cells; and that there is a strong correlation between the induction of chromosome aberrations and cell reproductive death in mammalian cells. These results provide a deeper understanding of the nature of the radiation induced molecular damage which is responsible for the biological effects. This understanding forms the

scientific base for the choice of dose-effect relationships assumed in the derivation of recommendations on exposure limits in radiological protection.

- Several contracts have examined the nature of radiation induced mutations in mammalian cells and have concluded that radiation rarely, if ever, induces point mutations but generally induces gross chromosomal alterations such as deletions or translocations. This is an important result because although chromosomal changes appear to be involved in the development of cancer, one recent result suggests that induction of a specific type of point mutation in an oncogene may also be a critical step in the multi-stage development of cancer. Thus radiation may be an incomplete or inefficiently complete carcinogenic agent.

- Another group of contracts have shown that the sensitivity of lymphocytes to the induction of dicentric chromosome aberrations varies between species and cannot be used as a general indicator of radiation sensitivity; that the direct comparison of chromosome damage induced in somatic cells with that induced in germ cells should be made with caution; that the radiation induced mutation frequency in mice is lower in a new set of specific locus mutations and enzyme-activity mutations than that found previously; and that in the mouse there is a low risk of chromosome loss associated with a surviving offspring after radiation. These results are all of direct relevance to assumptions, philosophies and values used in the current assessment of genetic risks of ionizing radiation.

2. REPAIR OF GENETIC DAMAGE IN PROKARYOTES AND EUKARYOTES

The aim of research on the repair of radiation damage is to identify crucial lesions and critical repair pathways to gain an understanding of the induction and expression of radiation damage at the cellular level. This in turn will provide support for the radiation protection philosophy chosen to extrapolate experimental radiobiology results and epidemiological analyses from high radiation doses to low doses of relevance to radiation protection.

Research in this area was designed to elucidate the biochemistry and genetics of the repair of the different lesions induced by ionizing radiation in the DNA molecule. Both UV and ionizing radiation are used in repair studies because they induce essentially different types of DNA damage and thus by comparison a wider approach to more repair pathways is achieved. Use was made of microorganisms which have a wide range of repair deficiencies and the methods developed for the microorganisms were applied to repair deficient and radiation sensitive eukaryotic cells such as yeast, mammalian and human cells. This research has been associated during the programme with a tremendous development in the use of modern molecular biological

methods which have been applied to a wide variety of problems demonstrating the ingenuity of the contractors and leading to some interesting and important results. It may be confidently anticipated that the further application of these techniques to the problems of DNA damage repair in the current programme will provide more information on the molecular nature of repair. Another important trend, clearly discernible, is an evolution of the research on repair starting from the studies in microorganisms to comparable studies in lower eukaryotic organisms, mammalian cells and human cells. Even though the genetics of the repair deficient mammalian and human cells is much less well defined than that of the microorganisms, several results from this evolution demonstrate the similarities between the DNA repair processes occurring in microorganisms and man. These results demonstrate the relevance of the work in microorganisms to that in human cells and thus provide the justification for the inclusion of work on prokaryotes in the Radiation Protection Programme.

2.1. The conservation of repair genes and enzymes during evolution

The fact that comparable repair genes and enzymes are found in a wide variety of species from microorganisms to man indicates the essential nature of the radiation repair mechanisms to the survival of the organism. This means that the information gained in previous radiation protection programmes on repair in micro-organisms, can usefully be extended and applied in the study of repair in human and mammalian cells.

The photoreactivation gene, which produces an enzyme that cleaves UV induced pyrimidine dimers under the influence of "blue light", has been isolated from E. coli and the 1416 nucleotide sequence of the gene has been determined (TNO, Rijswijk, 403; Univ., Rotterdam, 404). The photoreactivation gene from yeast has also been isolated and sequenced. At the DNA nucleotide level there appears to be little homology between the two genes but at the amino-acid level there is 35% homology, and when amino-acid similarity is taken into account this homology increases to 55%. This suggests that both genes have originated from a common ancestral gene. Photoreactivation deficient yeast cells have been transformed with a plasmid carrying the E. coli gene and have been shown to be capable of photoreactivation. This demonstrates that the E. coli gene can be functionally expressed in eukaryotic cells. A recA like gene, identified in the cyanobacterium Gloecapea alpicola, was subcloned in a plasmid and shown to be active in recA deficient E. coli (Univ. Coll., Galway, 415). The gene was sequenced and produced a protein with molecular weight of 41,000. Comparison of this protein with the E. coli RecA protein revealed more than 40% homology of the amino-acid locations.

The DNA polymerase enzymes alpha, beta and gamma, have been purified and compared in a wide range of organisms (Univ., Pavia, 428, 553; IRSC, Villejuif, 551). It has been found that the structure of the replicative DNA polymerase alpha has been highly

conserved during evolution and an active fragment of mol.wt. about 70,000 occurs in prokaryotes, eukaryotes and mitochondria. DNA ligases have been purified and have been found to exist in two separate classes, ligase I is found in mammalian cells and is suspected of being involved in DNA replication, whereas ligase II is thought to be the repair enzyme and appears to be strongly preserved during evolution as it is found in T4 bacteriophage, E.coli, yeast and mammalian cells.

2.2. Induced repair in micro-organisms and mammalian cells

It has been found that gamma radiation is an efficient inducer of recombination and mutagen but a poor inducer of SOS repair compared with UV light.

It has been shown that UV exposure of bacteria can induce a repair process which is error-prone in as much as it causes mutations and this repair process has been termed SOS repair. In E.coli induced mutagenesis is a consequence of the inactivation of the LexA protein and subsequent direct action of RecA protein (CNRS, Gif-sur-Yvette, 426). When intact phages are introduced into a UV-induced E.coli cell, mutations occur also in the intact phage. This effect is called "damage-site independent mutagenesis" and accounts for about half the total mutations caused by the induced error-prone repair.

Experimental results appear to corroborate the hypothesis that SOS-repair mutagenesis results from an inaccurate DNA synthesis giving mismatching of base pairs (Univ., Brussels, 359, 420, 548). In this case "damage-site independent" or untargeted mutations induced in undamaged phage should be subject to mismatch repair. In a mismatch repair deficient cell, more untargeted mutations should be found than in a wild type cell. The experiments did indeed show this result. It has been found that gamma-rays have a much lower efficiency for the induction of untargeted mutations than does UV. The uvr A, B and C genes and the ssb gene in E. coli are regulated by the recA-lexA dependent SOS repair system (Univ., Leiden, 408). Analysis of the cloned uvrA-ssb region showed that the genes are closely linked and both are regulated by the same SOS regulatory sequence. The uvrB gene is transcribed from two promoters both damage inducible. The uvrC gene is regulated by the recA-lexA SOS system but has different induction kinetics from the uvrA and uvrB genes.

In an examination of induced repair in mammalian cells use has been made of SV40 virus in monkey kidney cells, herpes simplex virus (HSV-1) in human diploid cells and parvovirus (H-1) in mammalian cells (IRSC, Villejuif, 427; Univ., Leiden, 405, 476; Univ., Brussels, 359). Treatment of monkey kidney host cells with a DNA damaging agent such as UV increases the survival (enhanced reactivation, ER) of UV irradiated SV40 viruses, and at the same time an enhanced mutagenesis (EM) of the progeny of the virus occurs. The mutations have been found to be single base pair substitutions located opposite pyrimidine dimer lesions. In human cells, HSV-1 virus was used to study enhanced reactivation

(ER) and enhanced mutagenesis (EM). ER was found in normal cells and in several complementation groups of repair deficient xeroderma pigmentosum (XP) patients, optimum ER occurred 1-2 days after exposure of the host cells to UV. Cells derived from some XP patients who had not developed cancer showed no ER. EM was found in all cells, including those cells not giving ER. It followed the same time course as ER except in the XP "variant" group of cells where EM was delayed with respect to ER. Thus ER and EM are inducible effects, responding to the same damage, but probably are different processes.

Several enzymes involved in the repair of DNA damage in mammalian cells were characterised (Biology Group, Ispra). A proof-reading exonuclease with a DNA editing function was identified and separated from DNA polymerase. This enzyme is probably used in error correction during DNA replication. An AP-endonuclease which cleaves the DNA strand at apurinic-apyrimidinic sites was partially purified. Its biological function is probably to introduce strand breaks in base damaged DNA. A DNA methyltransferase was partially purified from human placenta which was able to recognise cytosine residues for methylation of DNA. The enzyme showed a preference for hemimethylated CmG/GC form of CG dinucleotides, and this suggested that DNA methyl-transferases in differentiated animal tissue behave as "maintenance" and not as "de novo" DNA methylators.

2.3. Transfection of repair genes into repair deficient cells

In order to learn more about the specific nature of repair deficiencies and what makes a cell sensitive to radiation, DNA recombinant techniques have been used to clone DNA repair genes in a suitable vector, usually a plasmid, and to transfect repair deficient cells such that the repair gene is integrated into the genome of the repair deficient cell and corrects the repair defect. The aim is to integrate one copy of the repair gene stably into the repair deficient cell and have the repair gene active and expressed. In order to be able to select the transfected cells a marker gene is usually cloned together with the repair gene in the plasmid vector.

Using these techniques the photoreactivation gene of E.coli has been introduced into yeast cells and has been expressed to give photoreactivation (TNO, Rijswijk, 403). The yeast gene, when transfected into E. coli was not expressed. Mouse cells deficient in thymidine kinase activity (TK) were co-transfected using a plasmid carrying the HSV-1 gene for TK activity and another plasmid which gives rise to UV resistance. The TK gene was used to select transfected cells and the UV resistance of these mouse cells was investigated. Of nine transfectants, seven showed significantly higher UV resistance than the normal mouse cell. This resistance has been maintained for 80 generations. Two non-adjacent regions on the plasmid appear to be responsible for the UV resistance (Univ., Rome, 475). Attempts were made to introduce into XP cell lines the bacterial incision repair genes, uvrA and uvrB cloned in plasmid vectors. However, no complete

repair genes have been found in the transfected cells. Microinjection of the two proteins gave no correction of the repair deficiency in XP cells or in yeast cells (Univ., Leiden, 408).

Transfection using the human thymidine kinase gene (TK) and the hypoxanthine phosphoribosyl transferase (HPRT) gene into mouse cells deficient in these gene activities corrected the defect also when the HPRT gene came from the inactive human X chromosome (Univ., Rotterdam, 404; Univ., Leiden, 405). On the other hand attempts to transfect the gene to correct the defect in XP cells using DNA from wild type human cells failed, probably because only a very small amount of exogeneous DNA is incorporated into the genome of the XP cells. A human gene has been cloned which corrects a DNA repair defect in CHO cells, this is the first human repair gene isolated by DNA recombinant technology (Univ., Rotterdam, 404; Univ., Leiden, 405). Human and murine DNA has been co-transfected into radiation sensitive ataxia telangiectasia (A-T) cells. Transfectants were enriched by a series of selection procedures following irradiation. One clone has been found which has increased resistance to radiation and appears to be a true transformant. Similar studies using the UV sensitive XP cells were not successful (MRC, Brighton, 414).

Although the DNA recombinant techniques hold great promise for the isolation and identification of a series of repair genes crucial for the protection of an organism from radiation, success so far has been very limited and almost all attempts with human repair deficient cells have failed to achieve stable transfected colonies. As the state of art advances and new techniques become available further progress may be expected in this area.

2.4. Characteristics of repair deficient cells

Cells derived from humans suffering from some hereditary diseases are sensitive to radiation and other mutagenic agents. These people are usually cancer-prone and this demonstrates the relevance of DNA damage and its repair to the induction of cancer by radiation. Two groups of special interest to the Radiation Protection Programme are Ataxia telangiectasia (A-T), which is very sensitive to all ionizing radiation, and Xeroderma pigmentosum (XP), which is very sensitive to UV.

To date five different complementation groups have been identified in about ten families carrying A-T indicating considerable genetic heterogeneity (MRC, Chilton, 412; MRC, Brighton, 414; TNO, Rijswijk, 403; Univ., Rotterdam, 404). No repair of potentially lethal damage in plateau phase A-T cells has been found after irradiation compared with normal human fibroblast cells which appear to have a constitutive repair process showing no saturation at higher doses. When irradiated with more densely ionizing radiation, A-T cells show a lower relative RBE than normal cells. Using a plasmid carrying a gpt (guanine phosphotransferase) gene with enzyme induced double strand breaks in the DNA of the gpt gene, it was found that

normal cells efficiently repaired the double strand breaks with high fidelity while A-T cells showed a drastic reduction in the fidelity of repair. The misrepair made by A-T cells was in the form of deletions and rearrangements of the gpt gene. The results suggest that the A-T defect reduces the ability of the cells to repair dsb correctly. Using measurements of the post-irradiation repair of potentially lethal damage it has not been possible to identify A-T heterozygotes as the sensitivity and repair capability of these cells were normal. In a study of the repair of single and double strand breaks in A-T and normal cells it was shown that there was a rapid and slow repair of single strand breaks and that in some A-T cells the rapid repair was slower than in normal cells. Double strand breaks were also repaired at two rates, 50% of the breaks being repaired in 10 minutes after which a slower repair (about 1 hour) set in, both in A-T and normal cells. Double strand breaks induced by bleomycin are only slowly repaired and in some A-T cells more dsb were left unrepaired than in normal cells. It thus appears that the defect in A-T cells is more related to the correct repair of double strand breaks rather than with the rejoining of these breaks. This suggests that the induction and repair of DNA dsb are important factors determining the severity of a radiation effect.

Cells from Xeroderma pigmentosum (XP) patients are sensitive to UV radiation, and such patients are prone to skin cancer. Nine complementation groups have now been identified (Univ., Rotterdam, 404; Univ., Leiden, 405). Two genes on the human chromosome 1 have been identified which are involved in unscheduled DNA synthesis (UDS) which generally arises in the repair of UV damage. Attempts to correct the repair defect in XP cells using transfection techniques have not been successful. Injection of Micrococcus luteus UV endonuclease restored UDS in all XP cells, as did T4 endonuclease V. Both endonucleases catalyse only the incision of UV irradiated DNA, and it is concluded that all 9 complementation groups of XP are deficient in this incision step of repair.

The cell culture from one patient with immuno-deficiency symptoms (hypogammaglobulinaemia) proved to be radiation and mutagen sensitive. Delay in ligation of Okazaki fragments formed on DNA replication and in the sealing of breaks induced after dimethyl sulphonate treatment suggest that this cell may have a defect in ligation activity. These cells appear to be hypomutable when exposed to UV and gamma radiation so that they may be defective in error-prone repair processes (MRC, Brighton, 414).

Of twelve patients with Fanconi's Anaemia, two showed a hypersensitivity of lymphocytes to radiation as did also two patients with aplastic anaemia. When mitomycin C, a DNA cross-linking agent, was used cells from all Fanconi's Anaemia patients were hypersensitive, while the aplastic anaemia patients were not. Heterozygotes of Fanconi's Anaemia did not prove to be sensitive to mitomycin C (Univ., Leiden, 407).

Recently several mutants of Chinese hamster cells have been isolated which are sensitive to DNA damaging agents including ionizing radiation (MRC, Chilton, 412). These mutants are being studied because they display a wide range in repair defects resembling human repair deficient cell lines. Several CH-V79 and CHO mutants have been isolated with an enhanced sensitivity to X-rays. These mutants show no repair of potentially lethal damage in plateau phase, no dose rate effect and a relatively low RBE, and in these respects appear to be very similar to A-T cells. To study recombination in two of these radiation sensitive Chinese hamster cell lines, plasmids have been introduced carrying pairs of non-overlapping deletions in the bacterial gpt locus. In preliminary experiments a reduced ability to recombine these pairs of plasmids has been found compared to the recombination found in normal hamster cells (MRC, Chilton, 412).

2.5. Repair in yeast cells

Yeast is a useful system to use for the study of repair as its genetics are well defined and it provides a bridge from micro-organisms to mammalian cells.

A temperature sensitive mutant, which cannot ligate after excision resynthesis at the temperature of 37°C (restrictive temperature), was used to determine the repair of DNA damage. By comparing the number of breaks in cells held at the restrictive and permissive temperature the number of breaks attempting repair could be determined (Univ. Coll., Swansea, 411). In a study of repair in mitochondrial DNA several mutants have been isolated but among these there appear to be very few mutants which are deficient in the repair of mitochondrial DNA damage induced by gamma rays (UCL, Louvain, 410). In a study (Inst. Curie, Paris, 397) of the efficiency of DNA psoralen interstrand cross-links, monoadducts on DNA, or X-ray induced strand breaks, for mutagenic and recombinogenic activity, it was found that cross-links were 5 times more efficient than breaks or monoadducts. Previously it has been shown that mitotic recombination can be induced in yeast by radiation. Now it has been found that recombinants continue to form for up to 10 divisions after irradiation. It appears that some irradiated cells pass on this property to the progeny. An investigation of recombination in the cell cycle revealed that in cells irradiated in G1 recombination occurs before S. In excision deficient cells recombination occurs after replication in G2 when the probability of an event involving sister chromatids is 20 times greater than the probability of an event between chromosomes. In a continuous culture of yeast the induction rate of canavanine resistant cells increased as the dose rate of gamma radiation decreased (Univ., Giessen, 392). The mutant is thought to arise from recombination events and the results suggest an induction of this process by radiation. This was confirmed by applying an acute dose to a pre-exposed culture. This increased the mutation rate without affecting survival. Thus in yeast it would appear that radiation can induce a recombinational type of repair process.

3. GENETIC EFFECTS IN SOMATIC CELLS

Radiation damage to DNA in somatic cells is related to cell death, chromosomal aberrations and somatic mutations and can be associated with malignant transformation. The association between DNA damage and the cellular effects has been investigated in order to identify lesions responsible for the different effects. Plant cells have been used to study the induction of mutations, especially at low radiation doses, but the majority of the investigations have concerned mammalian, including human, cells where a large effort has shown that radiation-induced mutations more often involve chromosomal rearrangements and deletions than point mutations. Chromosomal aberrations have been mainly studied using lymphocytes which are readily accessible in animals and in man. Lymphocytes are suitable for the study of general mechanisms of radiation action and may provide a means of assessing the exposure history of a person. However, it appears that the direct extrapolation of damage in lymphocytes to damage in germ cells is not justified. Interesting work has been done using mammalian cells made permeable to restriction (DNA cutting) enzymes which showed that DNA double strand breaks are crucial to the formation of chromosomal aberrations.

3.1. DNA damage, repair and cytological effects

These studies are designed to investigate the relationship between radiation-induced DNA damage and the biological effects at the cellular level, to point up crucial lesions and provide support for assumptions made about dose effect relationships in current radiation protection philosophy.

A one-to-one relationship between DNA double strand breaks (dsb) and lethal events was found in yeast cells unable to repair dsb for a variety of different radiations from 20 Mev electrons to 2 kVp X-rays (GSF, Frankfurt, 394). In yeast cells both unrepaired and mis-repaired dsb may contribute to cell killing. Liquid holding recovery in survival after irradiation has been shown to be correlated with repair of dsb. It is concluded that an unrepaired dsb is lethal and that mis-repair of interacting dsb's can also be lethal. The repair of DNA strand breaks in Chinese hamster ovary cells after irradiation with X-rays or internal tritium rays at 0°C was followed as a function of time at 37°C (Univ., Hamburg, 391). The repair kinetics could be analysed into three different exponential components, I with a half-life of 2.5 minutes, II with a half-life of 15 minutes and III with a half-life of 200 minutes. I and II are thought to represent single strand break repair, III is thought to represent double strand break repair. The two radiation modalities induce different relative amounts of the three types of break. By comparing the cell survival after the two types of radiation with the relative break production, it was found that the cell killing could be associated with strand breaks of type III plus a contribution from the interaction of two class II single strand breaks. Sensitive methods for the detection of DNA damage have been

developed using immunochemical techniques, determination of repair synthesis, and measurement of strand breaks (TNO, Rijswijk, 403). In the immunochemical technique, small pieces of DNA are synthesised with a specific type of radiation damage, antibodies are produced which act against the damage and which are used to identify the damage in exposed cells. Single strand breaks are detected using alkaline elution through membrane filters followed by fluorimetric quantitation of DNA. Using the alkaline and neutral elution techniques, ssb and dsb were measured after gamma and neutron irradiation of human cells. Neutrons introduced only 30% of the ssb induced by the same dose of gamma rays, whereas the number of dsb was 160% of those induced by gamma rays. The repair kinetics of both ssb and dsb was similar following gamma rays and neutrons.

The distribution of UV induced repair patches along DNA loops attached to the nuclear matrix was examined using DNA degrading enzymes and neutral sucrose gradient centrifugation (Univ., Leiden, 407). The results suggest no association of repair with the nuclear matrix, a random distribution of repair patches along the DNA loops and simultaneous multiple incision events per loop. In contrast, in some XP cells the low level repair is preferentially associated with the nuclear matrix. A well defined eukaryotic gene isolated with its natural functional chromatin has been used to study radiation effects on the gene in vitro (Univ., Aarhus, 418). The direct ionization of the DNA is negligible when considering the inactivation of transcription. OH radicals are major inactivating species and an OER of 3 was measured. A sequence specific topoisomerase I (DNA unwinding) activity has been detected associated with chromatin, the binding sequence of the enzyme was found with high frequency in regulating regions in the genome and with regions known to be involved in specific recombinational events. The sequence specific topoisomerase I may play an important role in recombination and repair processes.

3.2. Studies on plants

Plants have proved to be a useful system for radiogenetic studies because well-defined gene loci determining specific functions can be investigated, because dose effect relationships can be followed to low doses and because conditions, such as oxygen tension, can be easily modified. The sensitivity of two different genotypes of tobacco plants to radiation-induced mutations of the a1-a2 system differed by a factor of more than three (Univ., Dijon, 419), and both dose effect relationships were approximately linear. Studies on in vitro cultures confirmed that most mutagenic events consist of deletions. Some experiments (Univ., Dijon, 419; Univ., Toulouse, 430) also used reversion of mutations of tobacco plants to determine the influence of small radiation doses and pollutants. Protoplasts isolated from different tissues of tobacco plants both at the haploid and the diploid level have been studied with respect to survival and mutagenesis (resistance to valine) (Biology Group, Ispra). Haploid cells were more radiosensitive than diploid ones

with respect to survival but about equally sensitive with respect to mutagenesis. A dose of 5 Gy caused an approximately 10 times increase in mutation rate. Survival of differentiated cells from leaves, most of them in the resting phase Go, is considerably more radiosensitive than that of actively dividing cells from young calli. Plants display great differences in radiosensitivity; thus protoplasts from carrots are about 10 times less sensitive than those from tobacco plants. The formation of transposable elements in maize is related to chromosome breaks which can also be produced by radiation (Univ., Köln, 396). In order to recognise such elements they had to be cloned and characterised. This was done for two mutants, both have similar but not identical DNA segments near the breakpoint. Translocations in the M1 generation after exposure to X-rays or fission neutrons were also investigated in another plant system, presoaked rye seeds (Landbouw H., Wageningen, 477). Only four translocations could be detected in each of the groups identified whereas many more translocations had been found in arabidopsis in similar studies. Genetic analysis reveals no difference between those induced by X-rays and those induced by neutrons with respect to frequency of breakpoint damage but neutrons might induce more severe local damage.

The induction of pink mutations in the stamen hairs of Tradescantia flowers has been used to study the interaction between X-rays and the chemical mutagen dibromoethane (DBE) (ITAL, Wageningen, 409). Six hour exposures to DBE were followed by acute X-ray doses. A more than additive effect was seen which increased the initial slope of the mutation induction curve at low doses. Simultaneous exposure to both agents over 12 hours also caused a more than additive effect at low doses of radiation. The chronic exposure to X-rays alone gave a linear dose relationship with no indication of a threshold dose down to 0.03 Gy. It was concluded that although a synergism was found the importance of this effect for radiological protection will depend on the cell's ability to repair the chemically induced DNA lesions.

3.3. Somatic mutations in mammalian cells

Cancer is the disease of particular concern in radiation protection and as somatic mutation is thought to be one important step in the early part of the development of cancer, a study of the nature of radiation induced mutations is of relevance to radiation protection.

An autoradiographic technique has been developed to detect hypoxanthine phosphoribosyl transferase (HPRT)-deficient mutants of Chinese hamster cells at the time of selection giving a clear identification of mutants after short expression times. This method improves the reliability of the mutation frequency determination and was also used to show that the mutations were complete (not "leaky") indicating that most were relatively large genetic changes. Alpha-particles had an RBE value for mutation frequency twice that found for cell killing while lower dose-rate

exposure to gamma rays reduced the mutation frequency parallel with the reduction in cell killing (MRC, Chilton, 412). Analysis of a series of mutants showed that radiation induced mutants lacked HPRT activity totally while 20% of ethyl methane sulphonate (EMS) induced mutations and 50% of spontaneous mutations had significant residual activity. None of the mutants lacked glucose-6 phosphate dehydrogenase (G6PD) activity from a gene closely linked to HPRT on the X chromosome. Most of the radiation induced mutations are not reversible compared with reversion of almost all of the chemically induced mutants. The data are all consistent with the suggestion that radiation induces large genetic changes such as deletions or rearrangements while chemicals such as EMS induce mainly point mutations. Human diploid skin fibroblasts have been found to synchronise and become stationary in G1 when held at 30°C; they can be stimulated to divide by raising the temperature to 37°C (Univ., Leiden, 407). The cells are able to repair dimers induced by UV at 30°C although the repair rate is reduced compared with that at 37°C. The mutation frequency in cells held in G1 after exposure was lower than that in cells exposed in S phase; thus the time available for excision repair between exposure and replication is the determining factor for mutation induction. The data show that these cells recover within about 10 hours from premutagenic damage induced by UV. Experiments using subpopulations of X-irradiated mouse lymphoma cells suggested the occurrence of untargeted mutagenesis, defined as an increase in the spontaneous mutation frequency at the HPRT gene in normal cells derived from irradiated parental cells (Univ., Leiden, 407). A larger experiment was designed to investigate this effect using three marker genes, HPRT, TK, and Oua. Initial measurements using the larger experiment and UV and X-rays have not provided any evidence for untargeted mutagenesis. The effects of photo-augmentation and photo-recovery from combined effects of near and far UV were investigated in mammalian cells. Photo-augmentation (a more than additive effect) was observed for survival when near UV (UVA) was given before far UV (UVB) (Univ., Leiden, 407). Photo-recovery (less than additive) was seen when UVB preceded or was given together with UVA. For mutation induction, a reduction was indicated for both combinations of UVA and UVB.

A mutational assay system has been developed for APRT (adenine phosphoribosyl transferase) locus in human diploid skin fibroblasts (Univ., Leiden, 406). The frequency of induction of the APRT-deficient mutants was found to be comparable to that for HPRT after X-rays. The long expression time of both mutants leads to doubts of the validity of the mutation frequencies measured. By measuring the mutation frequency for HPRT in two different ways, namely via the fluctuation test or the standard protocol, it has been shown that the mutation frequency determined with the standard protocol is reliable. The nature of HPRT mutants in mammalian cells was investigated. ENU (ethyl nitroso-urea) was efficient in reversing the chemically induced HPRT mutants and some spontaneous mutants, however X-rays were unable to reverse these mutants. An examination of the linkage between HPRT and G6PD in 23 spontaneous and 101 X-ray induced

mutants showed no evidence for the absence of G6PD, therefore deletions of HPRT also affecting G6PD are either unviable or very rare (Univ., Leiden, 406). The direct molecular analysis of the HPRT mutations became possible with a c-DNA probe of the HPRT gene. Using restriction enzyme mapping of DNA from mutants and wild type cells as well as hybridisation with the c-DNA, 6 bands of DNA from wild type cells were identified. More than half the 18 mutants analysed had an altered pattern of bands with loss of one or more bands. These results suggest that a large proportion of X-ray induced mutations are due to deletions.

3.4. Cytogenetics and radiation sensitivity

Cytogenetic studies on irradiated cells are useful to compare the radiosensitivity of different species, to recognise individuals of enhanced radiosensitivity and to assess past exposure history to clastogenic agents. The first aspect concerns the extrapolation of data measured in animals to predict comparable effects in man, the other two are relevant to the estimation of risk to special groups in the population. Information on the cytogenetic make-up of different species to be used for extrapolation purposes has been assembled in primates, carnivores, rodents and chiroptera. (CEA, Paris, 398). The ancestral karyotype is similar in rodents, primates and carnivores. Histograms were constructed showing the distribution of the half length of chromosomes in relation to the closer telomere or of the length of chromosome arms in relation to their centromere. These presentations also reflect the distribution of break points after treatment with a clastogenic agent. Radiation-induced break points are not random but vary from one type of rearrangement to another. Thus breakages near telomeres leading to dicentrics are relatively more frequent compared to other aberrations. This is most obvious in the chimpanzee and explains, for example, why the chimpanzee was considered a radiosensitive animal on the basis of dicentric production. It also follows that dicentrics do not reflect necessarily the situation for all types of aberrations and should be used with care to compare the radiosensitivity of different species.

Individuals who are predisposed to the development of cancer have been screened for small deletions and rearrangements using banding techniques (MRC, Edinburgh, 493) but no unexpected chromosome abnormalities could be detected. Experiments to elucidate the reasons for the greater chromosomal sensitivity of persons with Fanconi's anaemia have shown an increased production of superoxide ion in their erythrocytes (ENEL, Rome, 401). It is speculated that chromosome instability and radiation sensitivity are mediated via an activated oxygen species.

Several parameters of repair were studied in non-proliferating lymphocytes, UV induced DNA synthesis, UV tolerance (i.e. decrease in 7 day cell proliferation) and X-ray induced strand breaks (unwinding rate) (Finsen Inst., Copenhagen, 455). The UV responses displayed large seasonal variations and must be performed at the same time of the year for comparison. Patients

with multiple dermal cancer displayed a higher UV induced DNA synthesis and a lower UV tolerance. Rejoining of radiation-induced breaks during 2 hours was retarded in such patients previously exposed to UV or X-rays.

Whereas cytogenetic analysis readily allows the determination of homozygotes of chromosome breakage syndromes, heterozygotic conditions which may also display an increased radiosensitivity are much more difficult to detect (CEA, Paris, 398; Univ., Leiden, 407). Determination of in vitro radiosensitivity, enzymatic tests for breakage or determination of the length of cell cycle, have been explored but variability among heterozygotes and the general population is considerable. Progress of human spermatogenesis through meiosis was studied via three dimensional reconstructions of serial electron micrographs (Carlsberg Lab., Copenhagen, 417) in order to define sites and mechanisms of crossing over (about 70 per nucleus). A study of meiosis in the human female indicated that the length of time during which synaptonemal complexes exist and crossing-over can occur is shorter than in the male. Several years following radiotherapy for testicular cancer (0.35-1.08 Gy), pairing of chromosomes, behaviour of synaptonemal complexes and chromatin condensation were normal, and no indication for an altered meioitic recombination could be observed.

In order to explain the relation between genetic make-up and somatic radiosensitivity, 24 different mouse mutants in 27 different combinations were bred (MRC, Chilton, 429) for cytological screening (Univ., Leiden, 421). Micronuclei in bone marrow were determined after whole body irradiation (0.5 and 1 Gy). Micronucleus formation depends on the population exposed because of variations in response over the cell cycle, to delayed micronuclei formation and selective cell killing. Taking into account these factors, nine strains were found to range in radiosensitivity between normal mice and the known sensitive mutant MS/Ae.

Although tempting, extrapolation from the radiosensitivity of somatic lymphocytes to that of germ cells is not, in general, justified. This is shown by studies in mice with different chromosomal mutations (tertiary trisomics and T70H translocation heterozygotes) (Univ., Leiden, 406) where the yield of aberrations in germ cells was compared with that of chromosomal aberrations in the cultured lymphocytes.

3.5. Factors affecting genetic damage in somatic cells, particularly in lymphocytes

In some radiation protection situations it is desirable to have a means of estimating a potential accidental exposure. In most cases a measurement of the yield of chromosome aberrations in lymphocytes will be used. Several factors can influence the yield of aberrations in somatic cells such as treatment with inhibitors of repair, stage of cell cycle, radiation quality, temperature and culture conditions. These influences must be

known if lymphocytes are to be used to assess past radiation exposure.

DNA double strand breaks appear to be responsible for chromosome breaks (Univ., Leiden, 406) since post-X-irradiation treatment of permeable lymphocytes (and hamster ovary cells) with an endonuclease enzyme which converts single into double strand breaks increases all types of aberrations. After neutron irradiation no such increase is seen since few single strand breaks are present. The oxygen enhancement ratio for X-ray induced chromosomal aberrations is 1.5-2, that of sister chromatide exchanges (SCE) only 1. Since oxygen increases strand breaks but not base damage it is concluded that breaks are responsible for chromosome aberrations and base damage is responsible for SCE. Caffeine treatment which inhibits repair of potentially lethal damage increases chromosome aberrations but the extent varies from one person to another. In lymphocytes irradiated during the G2 phase, the percentage of cells undergoing mitotic delay decreases with dose, and those retarded in G2 display much fewer chromatid aberrations (Univ., Rome, 450). R banding techniques of delayed cells indicates that breaks on smaller chromosomes are preferentially located in the telomeric and centromeric region and in the junction between R+ and R- regions, and repair may thus occur in a non-random fashion. Lymphocytes cultured in the presence of tritiated thymidine which provides a low-level chronic beta radiation exposure and then exposed during S or G2 to X-rays develop fewer chromatid aberrations than expected from the total dose. It is conjectured that this lack of additivity results from an adaptive response similar to that seen after treatment with alkylating agents.

Three different cell lines in plateau phase have been used to study the effects of photon and fast neutron irradiation on cell reproductive death and dicentric and ring chromosome aberrations (TNO, Rijswijk, 300). In each cell line a constant ratio was observed between the induced cell reproductive death and the induced chromosome aberrations although the ratios were not the same for each cell line. When acentric fragments were also counted with the chromosome aberrations the ratio approached unity, and this suggests that gross chromosomal aberrations may account for the majority of cell reproductive death. No significant difference in the RBE values for the different effects was found. In measurements of cell transformation, it was concluded that transformation could arise from a specific type of chromosome aberration formed via a similar mechanism as the random aberrations. This would imply similar quantitative response to dose, dose rate and radiation quality. The effectiveness of different types of radiation, including ultra-soft X-rays, on the induction of cell reproductive death, mutation and chromosome aberrations has been studied in human and hamster cells (MRC, Chilton, 412). It has been found that the ultra-soft X-rays are very effective also at low doses giving an RBE of about 3 for all three biological endpoints. The results imply that a single localised electron track travelling less than

7 nm in the nucleus of the cell can produce the complete biological lesion for mutation, cell killing or chromosome aberrations. This result has serious implications for some radiation effects models and for the formation of chromosome exchanges since it means that either exchange takes place between two chromatids which are virtually in contact at the time of irradiation, or that only one chromatid needs to be damaged for an exchange to occur after irradiation. The studies on the influence of radiation quality on lymphocyte aberrations were continued (NRPB, Chilton, 413) using 9 MeV protons and 23 MeV He-3 nuclei. Data were analysed using the linear quadratic equation. The linear coefficents fall well into the humped LET-effect relationship found earlier. Comparison of acute with protracted Co-60 gamma irradiation demonstrates that the linear coefficient does not change with exposure time up to 6 hours whereas the quadratic coefficient decreases as expected, since repair has intervened.

Late repair could be studied in regenerating liver at different times after irradiation (Univ., Leiden, 406). The number of micronuclei induced in hepatocytes by X-rays decreased with the interval between irradiation and partial hepatectomy and attained control levels after 90 days but it remained high after 4.2 MeV neutrons indicating that the latter are not accessible to slow long term repair processes. The RBE in these experiments was about 4.

The yield of radiation-induced dicentrics in human lymphocytes increases with temperature in an S shaped fashion with a large increase at about 15°C (Univ., Göttingen, 570). Studies with temperature steps at different times from 1 minute to several hours before or after exposure show that only the temperature during exposure is decisive. Temperature acts as a dose modifying factor.

It has been reported that blood plasma from irradiated persons is clastogenic to normal lymphocytes and fibroblasts (Univ., Paris, 510), and a similar activity has also been observed in the plasma from persons with chronic inflammation or congenital breakage syndromes. This clastogenic factor seems to be related to the formation of superoxide radicals, can also be generated by xanthine+ xanthine oxidase or by treatment with tumour promoters and may be related to lipid peroxidation of cell membranes. The problem of clastogenic factors remains, however, a debatable subject.

3.6. Application of lymphocytes for biological dosimetry

Chromosome aberrations in lymphocytes can be used to provide a record of past exposure to mutagenic (clastogenic) agents and are therefore suitable also to determine radiation exposure either after an accident or under conditions of chronic occupational irradiation. Differences in cell cycle parameters of lymphocytes from different species explain many of the differences reported for radiosensitivity of the various species (CEN-SCK, Mol, 378).

In fact, most mammalian lymphocytes display comparable radiosensitivity when only first division cells are assayed. Moreover, remaining differences in the yield of dicentrics, i.e. the high one in chimpanzee, the low one in cat lymphocytes and the intermediate one in man, may be due to a particular organisation of the metaphase nucleus. If the dose is to be evaluated after partial body and/or fractionated exposure, the data on in vitro induction of chromosome aberrations in lymphocytes cannot be utilised directly (CEN-SCK, Mol, 378). Studies on patients undergoing radiotherapy for breast cancer indicate that the relative aberration yield is about proportional to the irradiated body volume.

The number of chromosome aberrations and micronuclei in lymphocytes was studied before and after heart catheterisation (Univ., Homburg, 289). Immediately after exposure (6-13 mGy) an increased number of micronuclei was observed; after 24 hours the rate had fallen but was still elevated. A similar pattern was observed also for chromosome aberration in heart catheterised children and in radio- therapy patients.

The effects of single and fractionated whole body exposure on chromosome aberrations in cultured lymphocytes of Macacca fascicularis were studied because the dose effect relationship in vitro resembles that of human lymphocytes (CEA, Fontenay-aux-Roses, 346). The yield of chromosome aberrations after a single acute whole body irradiation was similar to that after in vitro exposure and declined slowly over weeks. The decline was more pronounced when the dose was larger. Fractionation had additive effects. A lower dose rate of 1.3 mGy/min caused only half as many aberrations as a higher one (160 mGy/min). Changes in lymphocyte populations, differentiated by radioimmunoassay, may also be utilised for biological dosimetry (BGA, Neuherberg, 518). After irradiation in vitro the percentage of "null" cells increases, that of B lymphocytes decreases and that of T lymphocytes shows little change.

Several contractors (Chilton, Leiden, Mol, Edinburgh) participated in a study initiated by the IAEA to study the low dose response of lymphocytes. The frequency of dicentrics was reduced after doses of 4 mGy and did not appear to increase significantly after doses up to 50 mGy of X-rays. On the contrary, the neutron response was linear down to 10 mGy. Since the persons studied had a relatively high background level of aberrations, and this may have influenced the results, this study is now being extended and repeated under a new contract of the Radiation Protection Programme.

4. GENETIC EFFECTS IN GERM CELLS

4.1. Genetic studies on Drosophila

For over 50 years, Drosophila has been used in radiation genetics research since its genetics is well known and since it allows one

to study a large number of descendents in a short time. Drosophila is also the only system in which the consequences of specific repair defects in the parents on the yield of radiation induced mutations and chromosomal aberrations in the progeny - and thus not only a descendent cell - can be easily studied.

A Drosophila mutant which is defective in the repair of X-ray induced chromosome breakage events (Univ., Leiden, 406) displays an oxygen effect with respect to X-ray induced losses of ring-X chromosomes. In Drosophila males, genetic damage induced in earlier stages of spermatogenesis (spermatogonia to early spermatids) is subject to repair by paternal repair processes, while that induced in subsequent stages is subject to the operation of maternal repair processes. The influence of maternal repair processes on radiation-induced genetic damage in male germ cells was investigated using three repair-deficient mutants, two of which are post-replication repair deficient (mei-41 and mus-101)and one (mei-9) excision repair deficient. The results suggest that a significant proportion of pre-mutational lesions (presumably, that associated with chromosome breakage events) is lost via dominant lethality as a result of lack of repair. Further, by irradiating males in different gaseous atmospheres (nitrogen, air or oxygen) and studying their reparability with different repair deficient females, it was possible to show that radiation damage induced under anoxic conditions is qualitatively different from that induced in oxygen. It now appears possible to explain the radiation mutagenesis data obtained with the different repair-deficient strains on a unified bases (Univ., Leiden, 406).

A specific "mutator" gene in Drosophila increases spontaneous mutations (sex-linked lethals) and enhances the radiation effect. Specific mutations, many of them unstable, are also affected. By studying the reversion rate of a mutation, it was found that such a gene may constitute a "hot spot" for chromosome breakage. If such "hot spots" occurred also in man, the procedure of calculating doubling dose may not be valid since it is based on the assumption that radiation-induced mutations are qualitatively similar to those that arise spontaneously, and that there is a proportionality between spontaneous and induced mutation rates. Induction of specific locus mutations by 0.5 MeV neutrons or 100 KeV X-rays indicate an RBE of about 1.5 at high dose levels. Neutron irradiation causes a different mutation spectrum relative to that of X-rays in the sense that the contribution of chromosome breakage related to mutagenesis is higher with neutrons. Two Drosophila mutants with high frequency of spontaneous chromosome aberrations (Univ., Rome, 400, 450), if combined, prevent development beyond the larval stage. Apparently, different factors are involved in these mutations. One mutation affects mainly euchromatin, the other the euchromatic- heterochromatic junctions. Both increase the radiosensitivity to aberration induction by a factor of 2.5 to 3.

4.2. Genetic studies on mammals

Genetic risks arising from exposure of males to radiation result mainly from damage to spermatogonia, the permanent cell population from which all successive sperm cell stages are derived. Spermatogonia represent a highly heterogeneous population of variable radiosensitivity with respect to survival as well as with respect to mutagenesis and undergo several cell divisions during which unstable chromosomal damage can be eliminated before mature sperm develops. The extent and influence of these factors varies with the species, and this makes extrapolation from animals to man difficult. The principal genetic risks of radiation are non-disjunction of chromosomes, chromosomal aberrations and gene mutations. From the data presented it appears that non-disjunction compatible with viability is not a major risk from ionizing radiation although, again, differences between species and germ cell stages make such conclusions uncertain. Chromosomal damage that may be transmitted to the offspring are stable translocations and small deletions. The consequences of such lesions during development and later life require further study. A limited number of specific gene loci have been investigated for susceptibility to radiation-induced mutations. It appears that the spontaneous mutation frequency and the mutability of different genes varies much more than previously thought. Fortunately, the data suggest that mutability is, in general, lower than that indicated by the older data which have been used for risk assessment.

4.2.1. Radiosensitivity of male germ cells

Spermatogonia in mice represent a highly heterogeneous cell population of variable radiosensitivity as demonstrated by split dose experiments (MRC, Chilton, 453). An initial conditioning exposure triggers cell division and the appearance of sensitive cells after 24 hours. The triggered formerly radioresistant population becomes more sensitive with respect to specific locus mutations and cell killing than the formerly radiosensitive population and about equally sensitive with respect to translocations. After a few days, the cell population resistant to the induction of specific locus mutations or translocations is again re-established. The radiosensitivity pattern depends on the mouse strain probably because cell populations in the spermatogonia differ. On the other hand, such a sensitisation by split doses has not been observed for more differentiated spermatogonial stages (Univ., Leiden, 406). Different parameters of mouse spermatogenesis were studied after irradiation to provide a basis for evaluating biopsy material from irradiated human testes (Univ., Münster, 538). Reduction of S-phase cells, of primary spermatocytes, or of haploid germ cells, appeared to be most suitable to assess inactivation of germ cells, exposed as differentiated spermatogonia.

A dose dependent increase in diploid sperm and micronuclei, but no non-disjunction, were observed in male voles after irradiation with X-rays or 1 MeV neutrons (Univ., Leiden, 406). RBE values

were from 1.5-9.7 for diploid sperm and from 5.5-15.8 for micronuclei. These values as well as shape and slope of the dose effect relationships depended on the sperm cell stage irradiated.

4.2.2. Non-disjunction

Certain mouse chromosome arms involved in Robertsonian translocations show a particularly high degree of non-disjunction (MRC, Chilton, 457). Genetic markers have been established on these chromosomes to test non-disjunction and loss of specific chromosomes. A dose dependent increase in loss of chromosome 1 has been found for irradiated females or post-meiotic germ cells from males. Non-disjunction was observed in irradiated females but not in males irradiated at the spermatocyte stage. Non-disjunction of mouse chromosomes 11/13 as well as formation of micronuclei and DNA content (by flow cytometry) were studied in a mouse strain with a Robertsonian translocation (Landbouw H., Wageningen, 402). Formation of micronuclei appears not to be related to non-disjunction, and DNA measurements are not sufficiently accurate to estimate non-disjunction. It appears that certain chromosome mutants are much more sensitive to radiation-induced non-disjunction especially if exposed before metaphase I.

Non-disjunction was also studied after exposure of female mice either during the 15th day of gestation, prepubertal on day 7 of life or prior to ovulation (Univ., Göttingen, 393). No marked differences in the number of diploid oocytes were noted. A species with a higher incidence of spontaneous aneuploidy (Djungarian hamsters) yielded a dose dependent increase in diploid and hyperhaploid oocytes. Age at irradiation did not influence significantly the induction of structural anomalies but exposure of young mice had a more marked effect on precocious reduction in ovulation and hormonal functions tested by radioimmunoassay. Structural aberrations do not seem to depend on species (mouse, Chinese and Djungarian hamster) provided the same maturation phase was assayed.

The effects of radiation on non-disjunction and chromosome aberrations might be studied in human sperm following interspecies in vitro fertilisation (Univ. Coll., Galway, 514). This very delicate technique which uses hamster eggs freed from their zona pellucida and mixed with preincubated human sperm droplets still requires improvement. Experiments are now in progress using sperm from radiotherapy patients.

4.2.3. Translocations and deletions

Reciprocal translocations in rhesus monkey spermatogonia after single exposures from 0.25 to 8.5 Gy at a low dose rate (2 and 0.2 mGy/min), or after fractionated exposure, behave quite differently from those induced in mice (Univ., Leiden, 406). As shown by histological studies, monkey testis resembles human testis in its behaviour much more than does mouse testis, and thus may provide a more reliable basis for extrapolation. Tests

to study deletions on autosomal or X-chromosomes in the mouse were developed (MRC, Chilton, 452). A gene marker on the X-chromosome which can be detected in an albino background as heterozygotes by the UV fluorescence of the hair was followed in the descendents of females exposed to 1 Gy at the pronucleate stage or of males exposed at the postmeiotic stage. True deletions could not be observed, nearly all abnormal females found showed loss of the X chromosome. A test system for somatic mutations was developed based on the behaviour of melanocytes which can be used not only with embryos but also with adult animals. In both cases significant increases in mutation frequency were observed.

4.2.4. Mutations

Mutation rates in mice have been determined for a limited number of loci, and it is uncertain to which extent these are representative for other genes. The ratio of radiation-induced specific locus mutations to dominant cataracts (representing about 30 loci) varied from 6 to 36, dependent on the locus, with a weighted mean of 24 (GSF, Neuherberg, 395). This wide variability points out the need to estimate radiation-induced mutation rate from larger experiments and to analyse the dose response in detail. A genetic analysis of 17 cataract mutations revealed 12 with normal fertility and penetrance, the rest displayed reduced fertility and/or penetrance. A relatively high percentage of radiation-induced cataract mutations were homozygous lethal. Studies on a set of six new specific locus mutations (MRC, Chilton, 452), yielded a mutation rate of only about one fifth of that reported earlier by Russell using a similar fractionation regimen of 2 x 5 Gy, 24 hours apart. This is also somewhat lower than that reported earlier by the same laboratory. It appears, therefore, that the original set of specific locus mutations was much more mutable than the average mouse locus. Biochemical tests for mutations may allow the screening of large populations. Alterations in activity of 10 erythrocyte enzymes were compared with the specific locus test in mice (GSF, Neuherberg, 549). The rate of radiation-induced specific locus mutations was higher than that of enyzme activity mutations, perhaps because mutation frequency of recessive specific loci is extremely high compared to dominant enzyme alterations. This assumption seems to be supported by the data from dominant cataract mutations.

Assumptions concerning the normal mutation rate in man enter all genetic risk evaluations. This was studied (Univ., Giessen, 550) by electrophoresis of 10 blood proteins in blood samples routinely taken from new-born. More than 700,000 parental loci have been tested yielding 802 protein variants of which 4 turned out to be newly arisen in the new born.

4.2.5. Consequences of germ cell damage

The fate and consequences of chromosome aberrations induced in germ cells was studied in Syrian hamsters, a species which can

tolerate considerable chromatin imbalance (MRC, Chilton, 454). Improved techniques for the study of meiotic preparation showed how trivalent or univalent abnormalities can be transmitted to the early embryo. Aberrations are eliminated but unrelated chromosome changes also appear de novo until midgestation as shown by studies on embryos at midgestation and on hamsters at weaning. Studies on hamster cells, fibroblasts and lymphocytes using banding techniques indicate that even though chromosomes may show little disparity during replication they may still behave independently. Specific damage to late replicating chromatin (characteristic, for example, for alkylating agents) may be not as much a consequence of a specific action on certain chromosome segments than of an elimination of cells treated during early S phase. Model experiments on lymphocytes and fibroblasts were carried out to determine the proportion of radiation-induced reciprocal translocations which could lead to viable progeny (CEA, Paris, 398). Data on lymphocytes irradiated in Go suggest that about 2/5 of such translocations could result in a viable mono- or trisomy, and this is confirmed by studies on fibroblasts. Translocations might also be eliminated at later divisions, and this is now being studied. Analysis of changes induced in S phase indicates that they would rapidly lead to unbalanced arrangements of mono- or trisomy and very few balanced arrangements would be transmitted to subsequent generations.

5. PERSPECTIVES AND RECOMMENDATIONS

Over the five year period of the programme good progress has been made in all the areas covered by projects in the Genetics Sector. A start has been made in many laboratories to introduce the new molecular biology techniques in the study of radiation mutagenesis and repair. Although not all of these new experiments have been immediately successful there can be no doubt about the important contributions that these methods will provide in the future.

In other areas new biological technologies including monoclonal antibodies, chromosome identification, DNA damage measurements, mutant characterisation by protein analysis and reproductive cell biology have been refined to give improved accuracy and greater sensitivity. Some of the technologies have permitted the development of new experimental methods for the analysis of radiation induced cytological and genetic effects.

The biology of the spermatogenesis in man resembles in many respects that of primates. The equivalence of the biology of spermatogenesis between man and the experimental animal (primates) and the nature of the spontaneous and radiation induced mutations have been clearly identified as problem areas having a direct bearing on the extrapolation of experimental results to the assessment of genetic risk in man.

Steady and significant advances have been made towards a better understanding of the nature of the radiation induced damage, its

alleviation by repair, its transmission by cell division, its expression as a genetic effect and its impact on the organism. These are factors which have to be taken into account when predictions are to be made in radiation protection about the radiation sensitivity of various groups in the population, the appropriate choice of dose effect relationship for the estimation of low dose risk, and the potential genetic hazard of radiation to man.

Several specific recommendations can be made:

- repair studies should concentrate on repair processes in human and mammalian cells instead of prokaryotes.

- emphasis should be given to the identification of the lesions, mis-repair of which results in an increased radiation sensitivity rather than on the isolation of still more variant, possibly sensitive, cell lines.

- a thorough understanding of the critical repair pathways is desirable to indicate the nature of the crucial lesions and relate the occurrence of these with the cellular sensitivity to radiation.

- more information is needed on the shape of the dose effect relationship for chromosomal aberrations in lymphocytes at very low doses of sparsely ionizing radiation and also for different modalities of chronic exposure.

- a better comparison between the effectiveness of neutrons and other densely ionizing radiations and X-rays for the production of chromosomal aberrations is required together with information on similarities or differences in the nature of the induced aberrations.

- more work is needed on the induction of genetic effects in primates, where spermatogenesis is comparable with that in man.

- studies on the effects of radiation on oogenesis, preferably in primates, should be encouraged.

SECTOR F

EVALUATION OF RADIATION RISKS

RADIATION RISKS AND OPTIMISATION

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RADIATION RISKS AND OPTIMIZATION

1. PURPOSE AND GENERAL VIEW

In 1977, the International Commission on Radiological Protection published its new recommendations and these were addressed in the 1980 revision of the Basic Safety Standards for the health protection of the general public and workers against the dangers of ionizing radiation. The system is based on a risk and detriment concept requiring the assessment of realistic relationships between dosimetric data and environmental or biological effects, and is calling for full implementation of the ALARA principle. Therefore, research was oriented towards two different aspects: assessment of risks due to the presence or utilization of ionizing radiation and studies aiming at an optimization of radiological protection.

Over the past years, growing public awareness of the risks due to exposure from natural radioactivity, especially indoor exposure to radon and thoron daughter products, has become evident. An appraisal of its impact could only be obtained by determining mean exposures and dose distributions in order to locate "hot spots" and to devise cost-effective countermeasures.

The further implementation of the nuclear fuel cycle in the Member States revealed a strong public concern about the overall safety of these industrial activities which shifted towards preoccupation about the consequences of incidents and accidents. This led to the increasing application of probabilistic techniques for assessing the potential consequences and for designing appropriate mitigating actions.

Moreover, a tendency developed towards comparing risks of different industrial activities. The first comparative risk assessment studies were strongly contested though presently, a move towards realistic regional case studies is becoming apparent. They concern the application of radiological methodologies, in a mixed nuclear/non-nuclear field, in order to ensure maximum use of existing expertise and knowledge.

Optimization of radiological protection of the workers and the public required detailed analysis of occupational exposure data, dose distribution, and dose transfer between workers and the public. Cost-benefit analysis was applied to radioactive waste management and alternative approaches were investigated. Results of epidemiological studies are reported and alternative statistical procedures for their interpretation were developed.

2. RISKS DERIVED FROM EXPOSURE TO NATURAL RADIOACTIVITY

2.1. Introduction

Exposures to natural radiation are dominated by that arising indoors from inhalation of the decay products of the radioactive

gases radon and thoron. The major sources of indoor exposure are ingress of soil released radon, in most cases the predominant factor, and exhalation from some building materials, which show naturally high or artificially enhanced concentrations of radium.

In Europe, a widely used average indoor concentration of radon is about 20 $Bq.m^{-3}$ (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), Ionizing radiation: sources and biological effects, 1982), yielding a mean contribution to the total annual effective dose equivalent of about 30%. However in some cases these doses may be much higher, up to a hundred times the average, leading to an individual risk higher than that which can be accepted by the individual or by society.

The indoor radon concentration is correlated with the geological characteristics of the subsoil, though in a given region, dwellings erected near each other, sometimes show very different indoor levels of radon. The only way to identify the "dwellings at increased risk" is to carry out extensive survey programmes.

In order to improve the understanding of the parameters influencing indoor exposure, fundamental aspects like the attachment of radon daughter products to aerosol particles and exhalation from building materials and from the soil were studied. This was essential for implementing countermeasures to reduce the ingress of radon into the dwellings.

To establish optimal co-ordination of this European research, the Commission organized two meetings. The first meeting was entitled "Indoor exposure to natural radiation and related risk assessment", Anacapri, October 3-5, 1983, (reference is given in annex V) and the second "Exposure to enhanced natural radiation and its regulatory implications", Maastricht, March 25-27, 1985.

2.2. Intercomparison programmes of measurement techniques

Two intercomparison exercises for active and passive measuring devices were organized, the first one in 1982 and the second one in 1984 (NRPB, Chilton 500, 573). The first intercomparison of active techniques for measuring radon and its daughter products (Results of a quality assurance exercise for radon and radon decay product measurements; Report EUR 8629 EN) gave fairly good results (standard deviation of 10% on radon concentration and 15% on decay products). Closed passive dosemeters (response related solely to radon) showed good agreement (coefficient of variation 11%). The linearity of the response was excellent up to exposure levels of 2.7 $MBq.m^{-3}.h^{-1}$. Open passive dosemeters showed greater variability. Their accuracy greatly depended on the equilibrium factor: an intermediate equilibrium factor yielded results close to those of the active measurements, but with high or low equilibrium factors the results were less good (errors up to a factor 10). Although these dosemeters are intended to measure potential alpha energy, their response was more correlated with the radon concentration.

The second study (Results of the second CEC intercomparison of active and passive dosemeters for the measurement of radon and radon decay products; to be published as EUR report) followed the same pattern with 17 laboratories participating with passive dosemeters and 13 laboratories participating with an active measurement technique. The intercomparison was carried out as a Community participation in an international programme sponsored jointly by the CEC and the NEA (OECD). The results obtained with closed passive dosemeters proved that participants in both intercomparisons maintained their performance. Some new participants obtained high background track densities making the measurement of low exposures difficult. The performance of active measurement techniques of radon decay products improved, lowering the standard deviation from 15% in 1982 to 10% in 1984.

2.3. Parameters and modalities for assessing indoor exposure

Several environmental, physical and physiological parameters directly influence the exposure to radon. The geomorphological characteristics of the soil, its permeability, the existence of pressure, temperature and humidity gradients and lung deposition and clearance are some examples. Work was initiated on some of these factors.

Calculations have shown (Univ., Gent, 496) that the properties of the atmosphere largely determine the physical form of radioactive particles in the air. If condensable products are present, the size distribution of the radioactive ions not attached to the aerosol will broaden by clustering, i.e. the formation of microscopic droplets. It was shown that the classical description of airborne radioactivity in terms of an "unattached fraction" with a single diffusion coefficient and an "attached fraction" with a single activity median aerodynamic diameter of the aerosol (AMAD) is only valid for domestic environments free from freshly formed aerosols. This hampers simple extrapolation of laboratory data to real conditions and necessitates field measurements. The AMAD measured at three sites (NRPB, Chilton, 498) did not deviate much from the value of 0.17 μm adopted by ICRP for computing lung doses. At two sites, however, the AMAD was three times smaller which would result in a lung dose being 3 to 4 times higher than presently assumed.

Other factors also influence indoor exposure. An assessment of the time spent indoors revealed that the overall indoor occupancy factor is about 90%, with a global home occupancy factor of about 75% (NRPB, Chilton, 498). Ventilation will reduce the indoor radon concentration down to the outside level, though increases beyond 0.5 air renewals per hour are useless (CEA, Grenoble, 423 SC 007). Cracks and openings for ducts in solid floors enhance seepage of soil gas. A modified model of ingress to include mass transport due to pressure gradients was applied (NRPB, Chilton, 556). Some building materials contain naturally or technologically enhanced concentrations of natural radioactivity. Tiles and bricks used in Lombardie, Italy, showed high concentrations (CISE, Segrate, 495). Phosphogypsum appeared to

contain much radium (> 400 $Bq.kg^{-1}$) and its radon exhalation is two orders of magnitude higher than those observed for other materials (Univ., Gent, 496).

2.4. National and regional surveys

Most of the surveys on indoor radon concentration were conducted concurrently with surveys of environmental gamma exposure as the latter contributes about 30% of the total annual effective dose equivalent. The results of an intercomparison of environmental thermoluminescent dosemeters were discussed in the sector "Radiation dosimetry and its interpretation".

In the United Kingdom, (NRPB, Chilton, 498) a national survey was carried out as well as a regional one in areas where exposures might be expected to be above the average. The national survey encompassed over 2,000 houses: for bedrooms and living areas, a mean radon concentration of 17 and 24 $Bq.m^{-3}$ respectively and a mean gamma-ray dose rate in air of 0.5 and 0.6 $mGy.y^{-1}$ were observed. In Cornwall, an area having particular geomorphological characteristics, measurements revealed indoor gamma ray levels about 50% above the national average, and a mean radon concentration about 15 times the national value.

The national survey in Ireland (Univ. College, Dublin, 517) included approximately 220 dwellings. The selection of the surveyed dwellings was not at random, but focussed on areas where both the highest and the lowest values were expected. For penetrating radiation, the estimated median annual effective dose equivalent was 1 $mSv.y^{-1}$ (ranging from 0.4 to 1.4 $mSv.y^{-1}$). For radon, the median value was 40 $Bq.m^{-3}$ (ranging from 3 to 650 $Bq.m^{-3}$).

A regional study was carried out in the Federal Republic of Germany (Univ., Erlangen, 368). External exposure was measured by area monitoring and by using personal dosemeters. External radiation exposure was found to be about 0.42 $mSv.y^{-1}$. The mean annual effective dose equivalent due to radon was 0.59 $mSv.y^{-1}$, whereas a national mean value of around 1.2 $mSv.y^{-1}$ is presently assumed.

The survey carried out in France (CEA-CEN, Fontenay-aux-Roses, 319) yielded a mean value of 0.7 $mGy.y^{-1}$ for the indoor gamma exposure. The mean value of the radon concentration at the national level was about 25 $Bq.m^{-3}$.

In Italy, a survey focused on Milano and its surroundings (CISE, Segrate, 495) gave a mean value for penetrating radiation of 1 $mGy.y^{-1}$ and a mean value of the radon concentration of 30 $Bq.m^{-3}$. A national survey included about 500 dwellings (ENEA, Casaccia, 480) and indicated that the average radon concentration measured inside dwellings constructed with local tuff and aggregate blocks was about twice that observed in brick and stone dwellings. The mean radon concentration was 40 $Bq.m^{-3}$ (ranging from 4 to 330 $Bq.m^{-3}$). Gamma exposures showed a mean value of

0.9 $mGy.y^{-1}$; values greater than 1.8 $mGy.y^{-1}$ were only found around Bergamo where uranium mines are located and local building materials were used.

In Denmark, a pilot survey comprising 82 dwellings (Risø, Roskilde, 555) gave a mean value of 0.8 $mGy.y^{-1}$ for indoor gamma exposure. The mean value of the Rn-222 concentration in winter was about 90 $Bq.m^{-3}$ for the detached houses and 24 $Bq.m^{-3}$ for the flats; in the summer both were about 30% lower.

The Belgian survey (Univ. Gent, 496) comprised 80 houses. A mean value of 45 $Bq.m^{-3}$ for indoor radon concentration was found.

It must be emphasized that not all the surveys were organised in a unified way. Different patterns and phenomenological trends were observed and these hamper direct comparison. Anyhow, the data indicate clear regional differences due to the geological properties of the subsoil or to the building materials used locally.

Buildings with higher radon concentrations are hidden among a large number of buildings with normal radon concentrations. Therefore, from the point of view of cost-effectiveness, it seems more appropriate to use simple and cheap measuring devices but to perform the measurements in as many buildings as possible. Cost-benefit analysis of survey programmes indicated that at least 3% of the buildings should have an elevated radon concentration to render the survey cost effective(AIB, Solna, 423 SC 022).

2.5. Technological countermeasures

For existing dwellings, the first remedial action to consider is to limit the infiltration of the soil gas by sealing obvious ways of entry . Unfortunately, this is rarely possible since usually, infiltration is heterogeneous by nature and almost impossible to locate. Elimination of the convective flow of air into the building by depressurizing the soil or by breaking the capillarity layer under the basement slab reduced the indoor radon concentration by 80% (AIB, Solna, 423 SC 022). When radon from the soil enters a building through the crawl space, ventilation of the latter is indicated. Exhalation from building materials can be reduced by applying an epoxy paint or an aluminium foil on all accessible surfaces.

For new constructions, the approach is quite different and is based essentially on prevention. The use of building materials with strong radon exhalation can be avoided and the ingress of soil gas can be limited by minor modifications to conventional design, such as a ventilated crawl space with a monolithic slab treated with an air-proof material and a supply/exhaust ventilation system (AIB, Solna, 423 SC 022).

2.6. Conclusions

The intercomparisons, through the elimination of discrepancies, ensured higher reliability of the experimental results . Surveys indicated that the national mean values of indoor radon concentration do not directly cause a public health hazard with the exception of extreme values observed for particular regions or under particular conditions. With regard to the modelling of the ingress of radon from soil and the exposure parameters, there is a need for more sophisticated studies, especially on aerosol characteristics.

3. RISKS ASSOCIATED WITH PLANNED AND ACCIDENTAL RELEASES OF RADIOACTIVITY

3.1. Introduction

The total radiation risk to the population from the operation of a nuclear installation is the sum of two components: radiation exposure due to routine discharges and due to accidental releases of radioactive materials. There is a difference in the nature of these risks and in the way they need to be assessed.

The evaluation of the radiological consequences of normal releases in nuclear fuel cycle operations is needed for assessing the total health detriment and as an input into optimization studies. The occurrence of an accident cannot be predetermined but only predicted on a probabilistic basis; similarly the consequences of releases of radioactive material resulting from an accident, will vary considerably with the conditions pertaining at the time, for example meteorological conditions, season, location and habits of the population , etc.

3.2 Risks derived from normal operational releases

Exposure from routine discharges of effluents is maintained at very low levels by taking into account the general requirement: "as low as reasonably achievable" (ALARA). Several aspects of the methodologies for the evaluation and control of exposure from these effluents have been considered.

3.2.1 Cost-benefit analysis of waste treatment systems

The aim was to provide an insight into how judgement on the relative value assigned to future detriment can affect the result of optimization studies (NRPB, Chilton, 424). For long-lived nuclides, it is possible to calculate dose commitments extending over thousands of years. This detriment must be taken into account in present-day decision-making. A quantitative framework for the expression of such judgements was proposed, based on the economic principles of discounting, approximated by the use of incomplete collective dose commitments (cut-off).

3.2.2 Relative significance of the critical group and collective doses

In evaluating the radiological consequences of normal releases to the atmosphere (NRPB, Chilton, 424), two quantities are of particular interest: the dose to the critical group and the collective dose of the exposed population. The critical group dose enables a comparison with dose limits to be made and the collective dose provides a measure of the total potential health detriment. An evaluation was made of the extent to which the collective dose is effectively limited because of regulatory limits on critical group doses. Assuming that regulatory measures limit the critical group dose to less than 5 % of the dose limit, then the annual collective dose from airborne discharge would rarely exceed 1 man.Sv, essentially composed of very low individual doses. It was concluded that, given the range of monetary values presently assigned to the unit collective dose, no further cost effective reduction of doses below current regulatory levels of discharge must be envisaged.

3.2.3. Influence of discontinuities in routine releases on individual doses

The duration of a planned release influences the mode of calculating the dose. The analysis (NRPB, Chilton, 424) indicated that for a release of radioactive gasès lasting from one week to one month, individual doses in a year would be within a factor 2 of those resulting from a continuous discharge. However, for "pulsed" discharges lasting between a few minutes and 24 hours, differences of over two orders of magnitude are possible, particularly in case of rainfall. It was concluded that in these cases it is necessary to set both annual discharge limits and limits on the releases over shorter periods.

3.2.4. Mesoscale dispersion

A trajectory atmospheric dispersion model, MESOS (ICST, London, 423, SC 001) was adapted to represent realistically the temporal and spatial variability in the atmosphere over several hundred kilometres and to evaluate the resulting collective dose. Extensive meteorological and demographic data bases (Ass. Euratom-CEA, Fontenay-aux-Roses, 423) of Western Europe were used to assess the dilution and dispersion of normal releases over the required distances. Validation based on the 1957 Windscale release was carried out and proved that the MESOS model is able to estimate the changing mixing layer depth.

3.3. Risks derived from accidental releases

The methodologies for the assessment of the radiological consequences of accidental releases of radioactivity are increasingly being used for the analysis of risks presented by nuclear installations, for site selection and for the development of emergency planning arrangements. A two-year project on Methods for Assessing the Radiological Impact of Accidents

(MARIA) was initiated in 1983 and carried out jointly by two institutions (NRPB, Chilton, 542; KfK, Karlsruhe, 539). The goal was to make a comprehensive and up-to-date evaluation of the use of Probabilistic Risk Assessment (PRA) techniques in Accident Consequence Assessment (ACA). The different aspects presented in this section were presented at a CEC organized workshop on "Methods for Assessing the off-site Radiological Consequences of Nuclear Accidents", Luxembourg, April 15-19, 1985.

3.3.1. Atmospheric dispersion including topographical effects

Most models currently used for ACA do not take account of orographic or coastal effects on dispersion. An analysis and classification of the orography of German and British nuclear sites has been conducted in order to estimate the usefulness and importance of modelling topographical effects (NRPB, Chilton, 542; KfK, Karlsruhe, 539). Some sites showed such a degree of complexity that the prevailing methods of atmospheric dispersion modelling cannot be applied adequately. Models for dispersion at coastal sites have been reviewed for their applicability (NRPB, Chilton, 542; KfK, Karlsruhe, 539). No model adequately treating all aspects of the problem exists, e.g. the off-shore flow received little attention. An assessment of the likely change in predicted consequences, if allowance is made for coastal effects did not reveal a significant difference.

Deposition following an accidental release of radioactivity may be radically altered by precipitation, and models currently used for ACA are deficient in that respect. An alternative theoretical model has been developed in which the radioactive cloud is considered as a puff or assembly of puffs with isolated clouds advected at different wind speeds. Thus the spread of the pollutant along the wind is allowed for as well as the transverse spread, and the evolving overlap of the rain cloud and pollutant in relative motion over the ground is represented. Another aspect involved statistical distributions of contamination levels at remote receptor points for short accidental releases (ICST, London, 423 SC 001). The MESOS model is able to assess collective doses for short unplanned releases as the statistical procedure uses individual doses following contamination at discrete points.

3.3.2. Meteorological sampling scheme

Major parameters which influence the probability distribution of possible consequences are the meteorological conditions experienced by the dispersing activity. Using meteorological data from three sites, it was shown that the meteorological record used for the selection of weather sequences should be representative of the topographical location of the release (NRPB, Chilton, 542; KfK, Karlsruhe, 539). Seasonal variations of the atmospheric conditions appeared to have a much smaller impact on the consequences predicted, the same being true for the year-to-year variation of meteorological conditions. The procedure used to select the sample of weather sequences from the meteorological record should ensure both that infrequent,

potentially serious, sequences are not overlooked and that the sampling is capable of determining the probability with which each sequence occurs. It was concluded that stratified sampling was the most reliable procedure to meet these goals.

3.3.3 External exposure

If a radioactive cloud travels downwind, people will initially be exposed to external radiation from the cloud. For beta-irradiation, due to its short path length in air, semi-infinite cloud models are adequate for all applications. For gamma-irradiation, finite cloud models lead to greater precision in the predicted doses and despite the greater computing costs they are to be preferred for most applications of ACA.

Following dry and/or wet deposition, the shielding provided by buildings and surrounding structures leads to variations in external exposure. Three computer models (GRINDS, QAD-CG-E and DEPSHIELD) calculating the shielding properties of typical European building structures were compared (NRPB, Chilton 542; KfK, Karlsruhe, 539; Risø, Røskilde, 423 SC 014) and with the exception of a few special cases, the models are adequate for most situations of radiological interest and their results are in reasonable agreement.

3.3.4. Transfer of radionuclides through foodchains

The physical and physiological processes by which radionuclides are incorporated in foodchains are very complex and models are required to evaluate their environmental behaviour and to determine the distribution and retention of radionuclides in the body in order to calculate the subsequent radiation dose. In general it is sufficient to use metabolic models for a "reference man"; however, the uncertainties in dose estimates following ingestion may, in some cases, be a significant contribution to the overall uncertainty in ACA predictions.

The consequences for agriculture of an accidental release of radioactive materials to the atmosphere will vary depending upon the time of the year when the release occurs. Seasonal variations were studied (NRPB, Chilton, 542; KfK, Karlsruhe, 539) using the MARC-data for four representative times of release. The results show the considerable influence the season can have on the collective dose from ingestion of food, where no countermeasures are taken.

An evaluation of the effects of soil type, climate and agricultural practice on the transfer of some important radionuclides from soil to wheat (ICST, London, 499) showed that the greatest uptake occurred from the silt soil, with the least from the silty loam/loam, the latter being the soil with the highest total and per hectare production within the European Community. An assessment of the significance of the ingestion pathway (CEGB, Berkeley, 572) revealed that the ingestion dose was dominated by doses derived from I-131, Cs-134, Cs-137 in

green vegetables, fruit, cereals and milk and to a lesser extent from I-133 in milk.

3.3.5. Uncertainty analysis

The use of ACA as an input into decision making requires a move away from conservative modelling towards a more realistic approach, backed by uncertainty analysis to assess the overall reliability. This consists of a systematic procedure, using statistical methods, to quantify the confidence limits within which reality is expected to lie. Sensitivity and uncertainty analyses have been performed separately on a submodel basis to investigate the main sources of uncertainty (NRPB, Chilton, 542; KfK, Karlsruhe, 539). Overall uncertainty assessment of the complete ACA codes is needed in future to identify the major contributions and to provide insight into where future theoretical and experimental research might be most profitably directed.

3.3.6. Updating of European grids

In order to establish reliable assessments of individual and collective doses, and to evaluate the economical impact of accidental releases of radioactivity, European grids for several parameters (demography, agricultural produce, land use, etc.) were updated (Ass. Euratom-CEA, Fontenay-aux-Roses, 423). For preparing the land-use grid, an evaluation of the possibilities offered by satellite images was done (IABG, Ottobrunn, 423 SC 021). A comparison of the results obtained by the use of this innovative approach and the conventional exploitation of inquiries proved its reliability. Systematic exploitation of the satellite pictures will make it possible to perform regular updating of the land-use data for the whole territory of the European Community.

3.3.7 Marine environment

The long term and long distance behaviour of radioactive effluents, determined by residual circulation, were studied (Univ. Liège, 423 SC 012). Transport rates of particles and the dispersion of Cs-137 arising from the continuous release from Sellafield and la Hague were evaluated by means of an advection/diffusion model. The distribution of Cs-137 and Sb-125 in the Channel and in the Irish sea was studied (CEA-CEN, La Hague, 423 SC 013), and a comparative analysis of hydrodynamic models for releases in marine regions was conducted (LSEES, Fontenay-aux-Roses, 423 SC 006). It was concluded that while hydrodynamic models for each region are available (Channel, North Sea, ...) none exist for the whole of the North European waters.

3.3.8. Urban Environment

To assess the consequences of accidental releases in an urban environment important processes like deposition, resuspension, run-off, etc. have to be known. A comprehensive methodology to

enable more accurate dose predictions was developed (RISØ, Roskilde, 423 SC 014). Dry deposition velocities in urban areas are considerably smaller than those measured in rural areas. It was previously assumed that the concentration of radionuclides in the run-off water would be equal to the one in the rain-water; this is not true. Less contamination stuck to silicon-treated material than to porous red-tile roofing material and the measurements on old material indicated that 44 to 86 % of Cs-137 was removed by run-off, whereas for new material only 31 to 50 % was eliminated. Further measurements are needed in order to confirm the experimental results and to study the dependence on rain intensity.

Tracer experiments were carried out to assess the filtering effect of houses because the dose from inhalation can be reduced by staying indoors during a plume passage. A protection factor exceeding 10 can be reached. Several experiments were carried out to assess the efficiency of forced decontamination. A factor of up to 2 is reported for firehosing a road. Shielding factors for gamma-radiation from activity deposited on structures and ground surfaces for detached houses and multi-story buildings in several European countries showed a wide range (0.03 up to 0.4) around the average value used in the WASH 1400 code (0.2). In order to improve determination of the shielding factors, a systematic study of the characteristics of dwellings typical of urban areas was undertaken (EPFP, Sceaux, 423 SC 017).

The risk due to the accidental release of radioactive material near to a large population centre was assessed (NRC, Athens, 557); the models apply to the special Greek situation (Athens with 32% of the population of the country) but can be extended to other regions. It was concluded that reactors located within or near a large population centre should be equipped with special safeguards in order to protect the public from low probability/high consequence events and that sites with favourable wind roses must be selected.

3.3.9. Economic impact

Socio-economic consequences are important and a model was developed to evaluate the economic impact and the cost of emergency countermeasures (NRPB, Chilton, 424). The economic cost of evacuation/relocation and agricultural food restrictions served as input in the judgement of emergency planning and plant siting. The analysis demonstrated that techniques of ACA can be used to assist in the ranking of preferred sites. Parameters of particular importance are the incidence of early deaths, and the number of people and area of land affected by the application of countermeasures. The model can also be used as an aid to determine how much should be spent on emergency countermeasures to mitigate health consequences.

3.4. Conclusions

The increasing applications of ACA justify and require further research and development in the field of ACA modelling. This should help to make the outcome of an ACA more realistic and should reduce the uncertainties to such a level that probabilistic studies produce more reliable results. For atmospheric dispersion modelling, work is required on the influence of building effects, wind trajectories and topographic aspects. Stratified sampling of meteorological data was shown to be the most reliable procedure. More work has to be done in order to determine shielding coefficients for a passing cloud. Uncertainty analysis must be continued in order to assess the overall reliability of predicted consequences, including the economical cost of countermeasures.

4. COMPARATIVE RISK ASSESSMENT STUDIES

4.1. Introduction

Radiation protection research has yielded useful methods for assessing risks to man and his environment from the use of radioactive materials. The experience and knowledge thus gained, as well as the methods developed, are suitable for application in a broader context to prevent, reduce and manage risks derived from non-radioactive pollutants. Sound and coherent application of these methods, though hampered by the lack of an objective and universal index of harm, will enable a particular risk to be placed in perspective with other risks that society encounters. This can be used for policy decisions, for regulatory actions, and for public information. Ultimately, due consideration of low probability/high consequence events is essential in decision making processes on options in the development and regulation of technological activities. The potential inaccuracy of judgements related to these events is of particular concern and an adequate evaluation of the importance of handling uncertainties is essential.

4.2. Results

A study dealing with comparative risk assessment aimed at assessing and localizing in an objective way the extent of hazards and detrimental effects inherent in industrial nuclear and non-nuclear activities of the "Greater-Rhône-Delta" (CEDHYS, Fontenay-aux-Roses, 320). This region was selected because of its very high concentration of nuclear activities including all the steps of the fuel cycle, of its large number of conventional power plants (coal, oil, gas) and of its other major industrial activities (e.g. oil refineries).

Full characterization and description of the region was necessary. A complete data bank was created, making use of information of varying nature and origin. Sources of pollution were classified and the emissions were quantified through

bibliographical research, data collection and experimental validation. The exploitation phase was limited to an evaluation of the main risks of the normal operation of power plants, more emphasis being given to nuclear risks.

For electricity generating cycles, exposures due to atmospheric and liquid discharges were assessed for both the public and the workers. For public exposure, the local and regional impact was assessed for hypothetical individuals having maximum exposure (assuming total accumulation of the pollutant in one grid) and for the global population (collective exposure). Conventional atmospheric dispersion models and a hydrological model of the river considering nine sections with constant hydrodynamic characteristics were used. The combined release of radioactive materials by the different electricity generating cycles yielded a maximum annual individual exposure of $7.2\ 10^{-2}$ mSv, fossil fuel plants contributing less than 1 %. The computed annual collective dose was 5 man.Sv.

In the case of chemical effluents from the 3 fossil energy cycles, only the air concentrations or quantities accumulated by the organism were used. Comparing the computed data with authorized values or levels, an idea of their impact was gained. For exposure of the critical group to SO_2, the computed concentration is a factor of 20 lower than the authorized level; and several orders of magnitude lower for aerosols, cadmium, chromium, nickel and vanadium.

In case of liquid effluents from nuclear plants, only radioactive elements were considered. The annual individual exposure of the hypothetical group was 2.10^{-3} mSv and the annual collective dose equalled 4 man.Sv. Collective exposure data indicated the importance of the consumption of agricultural products grown with irrigation (60% of the collective dose).

For exposure of the workers, three categories were considered: radiation exposure and exposure to chemical and physical agents, based on statistical data on occupational diseases. In case of accidents (mining activities excluded), an analysis of the causes showed that less than 10% are due to the implemented technology, human failure being mostly the origin.

For the whole region, a balence-sheet of medical exposure (excluding screening programmes and dental radiography) was prepared. The collective dose adds up to 3,513 man.Sv. With regard to exposure to natural radioactivity, outdoor external irradiation was less than 1 $mGy.y^{-1}$ (national average being 0.7); indoor external irradiation was roughly of the same level; the radon concentration indoors varied between 4 and 900 $Bq.m^{-3}$ (national average of about 25 $Bq.m^{-3}$).

4.3. Conclusions

Comparative risk assessment, being a rather new subject of research, is hampered by numerous lacunas. For example neither the impact of chemical medication nor the natural exposure to chemical agents (heavy metals) or to non-ionizing radiation (U.V.) were considered. However, the study undertaken over the past years successfully applied a typically "radiation protection" approach to mixed "nuclear/non-nuclear" industrial activities. This was a pioneering approach and more data bases and methodologies are needed. Two recommendation can be formulated: (i) given the inherent uncertainties of the computed health effects, current emphasis must be on further updating of source term data; (ii) the results are a valuable tool for sound decision-making on industrial alternatives. In future voluntary and non-voluntary risks and cost-benefit analyses will have to be duly considered. The approach will contribute to the identification of areas where complementary research is needed, thus improving overall management of research resources.

5. ASSESSMENT OF OCCUPATIONAL EXPOSURE

5.1. Introduction

Careful analysis of occupational exposure data is essential for optimizing the radiological protection of the worker, for a more realistic planning of the monitoring of the working environment and for a better organization of the work.

5.2. Results

Radon in underground mines is the most important source of occupational exposure of miners. An evaluation of the factors influencing the radon emission in non-uraniferous underground mines (CEA, Fontenay-aux-Roses, 554) revealed that the parietal flux was more important than expected. Elimination of diffusive parietal fluxes in a fractured geological formation with high permeability was proved to be possible.

Occupational exposure in Pressurized Water Reactor (PWR) plants (CEPN, Fontenay-aux-Roses, 444) was evaluated. It was shown that: (i) the largest part (over 80%) of the total annual doses is to be attributed to the planned outage for maintenance and refuelling; (ii) steam generators' maintenance work and tasks associated with job preparation, cleaning and decontamination accounted for 50 to 60% of the collective dose; (iii) the mean irradiation level by components and circuits due to the deposition of activated corrosion products slowly increased (85% is due to cobalt isotopes). These conclusions for the highly standardized French power plants were confirmed by a limited survey of differently designed plants in Belgium, The Netherlands, Sweden and Finland indicating that collective doses are rather independent from the size of the units, but are strongly sensitive to design features.

Occupational exposure of the medical staff was analysed for a neuroradiology department (CEPN, Fontenay-aux-Roses, 423 SC 015). A model was established to allocate to each type of radiological examination an individual and collective dose for the staff involved. Seventeen types of examinations, accounting for 96% of the total activity, were used in the implementation of the model. The ambient radiation was measured at different places in the treatment rooms. Computed individual doses per examination were summed up and compared with the corresponding ambient radiation measurements. For different treatment rooms, the computed data were lower by 2 to 18%. This slight difference proved the validity of the modelling approach. For collective doses, the differences were more pronounced. In the case of anesthesists and physicians, the computed data were 20% to 40% higher than the results of the monthly integrated personal dosemeter readings, whereas for operators, the computed dose was two times less. The study demonstrated that an adequate modelling approach enables the identification of the principal causes of irradiation of the staff and permits a more rational approach for implementing additional protection measures.

Occupational exposure data for medical work places with registered individual doses above the mean were identified (GSF, Neuherberg, 458) and analysed in view of the determination of work place specific conversion factors between individual dose and effective dose equivalent. In brachytherapy, the conversion factors are strongly dependent on the type of work whereas in nuclear medicine, they mainly depend on the radionuclide used. Statistical data evaluation of values stored in the German Personal Monitoring Service was performed. Exposed radiologists (having at least one monthly dose exceeding the 0.1 mSv detection limit of the personal dosemeter) showed an increase from 1.2 mSv in 1979 up to 1.7 mSv in 1983; in nuclear medicine, the annual dose scattered around 2.2 mSv and for nuclear power plants, the annual dose decreased from 6.1 mSv down to 4.2 mSv.

5.3. Conclusion

Analysis of occupational exposure data is a prerequisite for further implementation of the ALARA principle. Further harmonization of data collection and data handling must be encouraged to enable reliable comparisons of the exposure data.

6. OPTIMIZATION OF RADIOLOGICAL PROTECTION

6.1. Introduction

Over the period considered, the recommendations put forward in publication 26 of ICRP and in the Basic safety standards were implemented. Most problems were related to the practical implementation of the optimization principle (ALARA) and the use of cost-benefit approaches.

6.2. Results

With regard to the definition of occupational health hazards, a case study was done on uranium extraction in non-sedimentary mines (CEPN, Fontenay-aux-Roses, 423 SC 003). The effective dose equivalent due to the inhalation of radon and its daughter products was higher than previously admitted and an examination of new radiological protection options was necessary. Cost-efficiency analysis was used to rank them. The value of the man.Sv for each option was computed and this led to a ranking within which the current level of protection was localized (640.000 FF per man.Sv).

Concerning public health, a case study on the protection against emissions of vinyl-chloride was carried out (CEPN, Fontenay-aux-Roses, 423 SC 004). Four plants with different emission abatement technologies were compared through a computation of avoided health effects and derived man.Sv values, and these values were put into perspective with the corresponding values for a 1,300 MWe nuclear power reactor. The analysis revealed strong discrepancies amongst the different plants and, for more recent plants, values of the man.Sv were significantly higher (up to a factor 40) than those computed for the nuclear plant. This was explained as the consequence of using "Best Available Technologies" instead of ALARA technologies.

The variability of individual doses as a factor in the assessment of the cost of the man.Sv was also studied (LSEES, Fontenay-aux-Roses, 423 SC 005). The reason to undertake this study was the central role accorded to the collective dose in the optimization procedure, disregarding the real individual risk. The individual risk could be addressed properly by applying more complex optimization procedures based on biological reasons (the shape of the dose-effect curve) or on decision criteria (relative importance of low and high doses, more equitable dose distribution). Two methods can be used: the use of a beta term, i.e. the subjective detriment (as proposed by ICRP) or a summation of alpha terms, i.e. the objective detriment, for different individual exposures (as proposed by NRPB). Being mathematically equivalent approaches, the latter method is simpler and was applied. Ideally, the monetary value of the different levels of exposure must be an increasing function of dose. For simplification, it is preferable to work with ranges of exposure and to define a step function for fixing the corresponding values of alpha. Application to two different cases, public exposure around a nuclear plant and occupational exposure of uranium miners, demonstrated the feasibility of the approach, though it is doubtful whether such a complex method is necessary for low level exposure of the public.

The long-term implications of the radiological detriment were appraised in a case study of long-lived wastes (CEPN, Fontenay-aux-Roses, 423 SC 010) for which dose commitments over thousands or millions of years can be computed. Inclusion of the detriment to future generations in present day decision making

requires judgement to be made. If the ICRP approach containing the alpha and beta term is used, the consideration of the long-term impact has different implications for each of them. For the alpha term, economical discounting techniques can be used, whereas for the beta term, a step function is more appropriate to include the risk perception by future generations. In case of low risks and reduced costs of protection, a simpler method is recommended; in case of high long term risks, multi-criterium analysis is indicated; and in intermediate cases, the simplified cost-benefit analysis is proposed.

Cost determinants of the radiological detriment were analysed (CEPN, Fontenay-aux-Roses, 423 SC 020) because the application of cost-benefit analysis requires a monetary value for the radiological detriment. Two methods are available: a priori fixation of the value of human life based on the principle of the "human capital" or a posteriori fixation through an estimation of costs and efficiency of risk reduction measures. Analysis of these values shows differences exceeding 4 orders of magnitude. The psychosocial, technical, economical and decisional determinants underlying risk reduction policies were investigated. It was shown that they explain the observed differences and that, at the same time, an a priori fixed value of human life was not used to orient the different options. Risk management is a very complex process and, as a consequence, different values of human life in function of the activity, the habits, etc. in a given country can be acceptable, though it may be desirable to reduce the variations. The theoretical bases for a sound analysis exist and the different determinants must be considered in risk management strategies.

A practical example of optimization of radiological protection has been made for a planned emergency clean-up system of a tritium handling laboratory (JCR, Ispra, 423 SC 023). Conservative assumptions with regard to released quantities and meteorological conditions were used. With regard to public exposure, the maximum individual doses for both chemical forms (HT and HTO) and for all four options remained far below the limits. The maximum avoided collective dose was about 260 man.mSv, and using an extremely high value of 1.10^6 US$ per man.Sv, the maximum investment cost should therefore not exceed $0.3.10^6$ ECU, which strongly contrasts with the estimated investment cost of $1.7.10^6$ ECU. With regard to the exposure of the workers, the occupational exposure only becomes important in case of HTO releases. Individual occupational exposure will exceed the usual 50 mSv limit following a HTO release exceeding 0.5 g. It was therefore concluded that shifting part of the projected investment to improve the protection of the workers is more cost-effective.

Biostatistical tools were applied to evaluate single risk factors and to improve knowledge on interactive situations of ionizing radiation and co-factors (CEPN, Fontenay-aux-Roses, 423, SC 011). An interaction being indicated was exposure to radon and smoking among uranium workers.

6.3. Conclusion

These results contribute to a further implementation of the optimization procedure and application of cost-benefit analysis, and to the elaboration and testing of alternative approaches in optimizing radiological protection of both the public and the workers. More emphasis has to be put on individual dose distributions.

7. RISK ASSESSMENT FROM EPIDEMIOLOGICAL DATA

7.1. Introduction

Important information on risks can be gained from the study of selected populations exposed to technologically enhanced natural radioactivity, or exposed occupationally, accidentally or for medical reasons. Data collection regarding human populations is the most direct way of estimating risk coefficients for intermediate and low exposure.

7.2. Results

A feasibility study was carried out (Inserm, Villejuif, 445) in order to evaluate the possibility of associating birth defects with the occurrence of a pelvic radiodiagnostic examination of the man prior to the conception of the child. From the estimates provided (for the Paris area, in 6 months, 1204 radiodiagnostic pelvic examinations were followed within 2 months by conception) it appeared that the approach is realistic enough to make a cohort epidemiological study of birthweight a serious proposition. Statistical evaluation has shown that a study and control cohort of 700 cases allows the detection of a 100 g shift in birthweight.

A re-examination of the British data concerning the relationship between diagnostic radiation during pregnancy and subsequent cancer in the child was performed (Univ., Birmingham, 541). The tests carried out allowed comprehensively for the effects of confounding variables and excluded any general bias of recall or ascertainment between cases and controls. The analyses showed that the confounding variables tended to mask rather than to exaggerate the full effects of radiation during pregnancy. Overall, the corrected estimate for relative risk following foetal radiation is about 2.2, compared with earlier crude estimates of about 1.5.

Another specific follow-up study was done on the dose-effect relationship of X-ray therapy to the head and neck area (MSRB, Dublin, 423 SC 008). The long-term effect of radiotherapy for seborrhoeic and other conditions of the skin of the face have been studied. A significantly greater than expected number of cancers of the head and neck, and particularly of buccal cavity and pharynx cancer, occurred in about 10,000 patients treated 15

to 50 years earlier with radiotherapy for acne, other skin conditions, and other disorders of the head and neck.

During the execution of the project reported above, coincidence led to the identification of some 500 persons in England and Wales who had received direct eye therapy (MSRB, Dublin, 423, SC 009, SC 016). Just over 200 persons could be traced. For 29 cataract patients, the mean latency period between therapy and first recorded cataract was assessed to be 19.5 years. It was also shown that radiotherapy increased the risk of a cataract almost fivefold.

An analysis was carried out in order to examine whether the substantial increase during the last decades of the number of radiodiagnostic examinations was followed by some carcinogenic effects measurable by an increase of the mortality of some specific radio-sensitive sites, in particular lung or breast (INSERM, Villejuif, 515). Therefore, analysis of spatial and temporal variations in the frequency of radiodiagnostic examinations and of incidence of certain types of cancers was carried out. Some confounding factors like industrial activities, and cigarette and alcohol consumption were taken into account. The results indicated that due to the high geographical correlation between cigarette smoking and frequency of radiodiagnostic examinations, it is not possible to separate their effects; breast cancer has been linked with the reproductive history of women and dietary factors (especially beer consumption) ; none of the industrial risk factors was significantly correlated with the frequency of radiodiagnostic examinations.

Dosimetric data obtainable from radiotherapy and from the atomic bomb survivors were analyzed and used for the development of a methodology (NRPB, Chilton, 337) to detect small excesses of radiation induced cancer. The methodology was validated through an analysis of the epidemiological data of the employees of the Hanford nuclear establishment in the USA. This indicated that those workers who died of multiple myeloma tended to have received higher doses, whereas there was no evidence of an excess of leukaemia cases. Another part of this study aimed at testing analytical techniques using simulated epidemiological data containing a number of "radiation induced cancers". One particularly important question was whether the risks of radiation are best modelled by an additive (or absolute) risk model or by a multiplicative (or relative) risk model. Application to data of the Atomic Bomb Survivors and patients receiving radiotherapy for ankylosing spondylitis showed that the multiplicative risk model generally gave better results.

There is a well-recognized problem in deciding the way in which different kinds of detriment should be combined to give an overall picture of the harm arising from any given hazard or practice. Comparative risk studies were therefore undertaken (NRPB, Chilton, 337). Even when attention is concentrated on fatal cancers as the most important late somatic effect of

exposure, there is no single statistic which completely represents the consequence of population exposures. Nevertheless, summarising statistics are important tools in understanding and comparing different sources of risk. Applying these approaches to several risks, it was concluded that the choice of an absolute or relative risk model may affect estimates of years of life lost even where total induced fatalities remain the same.

Thorotrast was used previously as X-ray contrast medium in many countries; the most complete follow-up of its consequences deals with 894 traced patients and 662 controls (DKFZ, Heidelberg, 369). The results were discussed at the symposium on "The radiobiology of radium and thorotrast", Neuherberg, October 29-31, 1984 (reference is given in annex IV). Among the 149 patients who died during the last 4 years and for whom exposure dated back to about 40 years, more than 50% suffered from primary liver cancer. The patients dying from liver cancer were significantly younger at the time of thorotrast application than the average. An excess of myeloproliferative diseases and pancreatic cancer was also observed, but bronchial cancer was not increased although the lung is constantly exposed to exhaled radioactive thoron. Among non-stochastic changes liver cirrhosis (often combined with liver cancer) showed a significant increase in the percentage of the deaths among the patients. Animal studies indicate that cancer is due to radiation exposure and not to a "foreign body effect" from thorium dioxide.

Quantification and evaluation of somatic radiation risks of low doses were assessed (GSF, Neuherberg, 422) through a determination of the exposure of members of the general public from natural sources and technological practices. The results showed that in the Federal Republic of Germany, the natural, the technologically enhanced and the medical radiation exposure each contribute about 1 mSv committed effective dose equivalent per year and per caput, every other contribution being at least two orders of magnitude smaller. The results also confirmed that under certain conditions, the exposure to radon-daughters in houses may constitute a real radiological health hazard.

The applicability of specific activity models for H-3 and C-14 was tested (GSF, Neuherberg, 422) and both proved to be reliable. For iodine and cesium isotopes, organ and eye specific dose factors and their variabilities were calculated, showing a significant variation with age. Dose factors for different target regions in the lung from inhaled radon-daughters were estimated for the occupational exposure of miners and for exposure of the general public. Moderate to low ventilation rates gave the most reliable assessment of lung doses to the general public.

In order to investigate the supposed increased rate of malformations of new born near a nuclear power plant, sensitivity to confounding factors, secular trends, etc. of various statistical methods was tested using a large epidemiological data set (GSF, Neuherberg, 422). No correlation was found but it was

shown that more weight should be given to the confirmation of epidemiological data before interpreting them in terms of dose effect relationships. Other epidemiological studies dealing with carcinogenesis have been reported in the sector "Late somatic effects of ionizing radiation".

7.3. Conclusions

Epidemiology is a field where a co-ordinated European effort is required and where a common approach regarding data collection and evaluation can greatly enhance the prospects of achieving worthwhile objectives. A common framework must be developed for radiation epidemiology, in particular for studies of the effects of low levels of exposure. Identification and description of sufficiently large populations and appropriate control populations, appreciation of their homogeneity, assessment of exposure and availability of existing records or data banks are necessary to demonstrate the feasibility of the planned work. With respect to the use of relative and absolute risk models, and also with respect to the definition of a universal index of harm, more exploratory studies are needed.

8. PERSPECTIVES AND RECOMMENDATIONS

Valuable data was obtained for the evaluation of risks derived from exposure to natural radioactivity, more particularly the radon and thoron daughter products. Further standardization of survey programmes is required in view of evaluating the feasibility of a large epidemiological study of indoor radon exposure and lung cancer induction. The largest uncertainty still persisting is the lung dose calculation. This necessitates studies of the physicochemical properties of the radon daughter products, their interaction with the prevailing indoor aerosol and their deposition in the humid airways of the human lung. A better understanding of these fundamental processes will contribute to the design of cost-effective countermeasures. Equally relevant are improved modelling of the ingress of soil-gas and of indoor exchanges of air, exhalation measurements of building materials and tests of procedures to reduce exhalation. Detailed studies are also needed to explain the poor correlation with the local geological characteristics which causes drastic differences of indoor radon concentrations in similar houses close to each other.

The risks associated with normal operational releases from nuclear installations, as well as those associated with waste products showing technologically enhanced levels of natural radioactivity, continue to deserve better quantification. Existing methodologies must be updated and due consideration of presently neglected pathways, e.g. the liquid discharges and consequent contamination of the food-chain, must be carried out.

Unplanned releases from nuclear installations and their consequences for man and his environment need further careful

assessment. The use of probabilistic techniques in the area of low probability/high consequence events must be elaborated. Within this context, uncertainty analysis carried out on the existing approaches has already indicated major gaps in present day knowledge. Mesoscale atmospheric dispersion modelling will have to include trajectory and subsequent puff models. The inclusion of topographic characteristics and full physical and radiochemical description of the source term becomes necessary. For a quantified assessment of the consequences, the urban environment deserves special attention. Deposition and resuspension of radioactive material, shielding effects of houses for deposited radioactivity and for a passing radioactive cloud, filtering effect of houses, natural weathering and forced decontamination of different surfaces, building wake effects and socio-economical consequences of contamination and countermeasures are examples where further work is needed. Continuous updating of the European grids on land use, agricultural procedure, demography, etc. will be needed. All methodological developments have to be done concurrently with systematic uncertainty analysis for ascertaining optimal use of resources.

Methods developed radiation protection and the available knowledge and expertise can be applied advantageously in approaches dealing with conventional pollutants. Comparative risk assessment studies carried out on a regional basis will contribute to sounder decision making and adequate risk management. The present efforts must be completed by including the contamination of surface waters and the probabilities of accidents and catastrophic events. Coherent application of these methods will allow risks to be placed in perspective with each other and may constitute an essential contribution in policy making, regulatory activities and information of the public.

Optimization of radiological protection of workers and the public and the further implementation of the ALARA principle laid down in the basic safety standards remain basic issues. Further harmonization of data occupational exposure collection and data handling will enable to make comparisons of exposures linked to certain practices or work places. Case studies describing the practical implementation of ALARA must be carried out. Decision aiding techniques other than cost-benefit analysis, i.e. cost-effectiveness analysis and multi-attribute analysis, have to be used in view of a selection of protection options.

A co-ordinated European effort for defining a common framework for epidemiological data collection and evaluation is required in order to achieve worthwhile objectives, especially for the low levels of exposure.

REDUCTION OF PATIENT EXPOSURE IN MEDICAL DIAGNOSTIC RADIOLOGY

1. PURPOSE AND GENERAL VIEW

Exposure to ionizing radiation is inherent to diagnostic radiology, nuclear medicine and associated medical practices. Large numbers of persons are involved and medical use of radiation even increases with improved health care. During the 1980-1984 period about 200.000.000 radiological examinations per year were carried out in the population of 270.000.000 in the European Member States, involving in many instances significant doses to individuals and constituting the greatest proportion of exposure to man-made irradiation. It is thus necessary to take care of the problems related to the radiation protection of the patient and the reduction of those doses.

This objective has been taken up on two levels, in a special "Council Directive laying down basic measures for the radiation protection of persons undergoing medical examination or treatment", of 3 Sept. 1984 (O.J. L 265 Vol. 27, 5 Oct. 1984), and in research to optimize the radiological procedures with a view to reduce unnecessary patient exposure, consistent with the production of the required diagnostic information.

In the 1980-1984 period, research concentrated on three main areas: assessment of the current radiological processes and practices; data on patient exposure for the various techniques and examinations; dose reduction including criteria and methods to be proposed for readily applicable quality assurance programmes. The research results achieved can assist the Member States to implement the Council Directive and to set up guidelines for improving patient protection in diagnostic radiology.

2. MAIN RESULTS

Research on reduction of patient exposure was a rather new area in the Radiation Protection Programme. The 10 participating laboratories could only progressively harmonize their working procedures and the presented results are not yet perfectly comparable. They contribute, however, to pinpoint the critical steps in the medical exposure to the population and to indicate a series of measures for optimizing diagnostic radiology.

2.1. Assessment of Radiological Practices

Surveys in four Member States contributed data to the evaluation of frequencies of radiological examinations and consequently of trends in exposure within the Community (CEPN, Fontenay-aux-Roses, 444 + 540; Osp. S. Maria Mis., Udine, 516; Nuclear Energy Board, Dublin, 449 and NRPB, Chilton, 497).

As the conditions of surveys differ in the Member States and even in the individual regions of one country, efforts must be made to

standardize the surveys by selecting similar criteria for their execution, e.g. representative number and type of examinations and measurements, test instrumentation and dose assessment. The results would then indicate more clearly the differences in habits and practices and would explain, at least partly, the differences among the obtained values.

2.1.1. General Situation

The number of X-ray examinations per 1000 persons per year (without dental radiology) was rather similar in France (836) and in the Friuli-Venezia-Giulia (FVG) Region in Northern Italy (745) and was essentially lower in Ireland (460). These results are confirmed by the mean number of exposures per examination, which is 2.2 in Ireland against 3.1 in the FVG Region and 3.6 in France. In this context it is noteworthy that in Ireland 99 % of diagnostic radiology is done in hospitals, while in France and in the FVG Region about half of the radiological examinations are done in private practices. The age distribution of the patients, examined by X-rays, plays an important role in the determination of risk factors. It is therefore interesting that in Ireland the relatively highest number of examinations took place in the age group between 20 and 40 years, while in other countries the older group (older than 45) was most frequently examined.

Population exposure and the possible expected detriment can be assessed based on various dose quantities such as the genetically significant dose (GSD), the somatically significant dose, often approached by the red bone marrow dose per caput (RBMD) and the effective dose equivalent per caput (EDE). There is still no consensus on the usefulness of these quantities, but each of them might help to describe trends and relative values specially if they were set up in the same way. Thus the limits of the validity of the EDE for medical exposure were pointed out and the importance for the research of more relevant risk coefficients was stressed (GSF, Neuherberg, 458).

The surveys allowed the evaluation of some of these quantities such as the GSD for France = 290 μSv and for the FVG Region = 248 μSv; the RBMD was determined for France = 743 μSv and for Ireland = 200 μSv; the EDE was calculated for France (taking into account 6 organs) = 463 μSv and for the FVG Region (6 organs + remainder) = 763 μSv.

In nuclear medicine a first survey has been carried out in the United Kingdom. A four fold increase of the number of examinations has been observed since 1973, but only 7 of 1000 inhabitants per year are examinated by nuclear medicine procedures compared to 550 per 1000 for X-rays. The effective doses for individual procedures was below 0.5 mSv for non imaging techniques and between 1 mSv and 10 mSv for imaging techniques.

2.1.2 Particular Radiological Examinations

Among the particular examinations two types received special attention: mammography, in view of its increasing application in screening programmes and the sensitivity of the tissues involved, and dental radiology, of which the single examination contributes only a small amount to patient exposure, but which is the most frequent individual examination and is carried out near sensitive organs such as the thyroid and the eye.

Surveys on mammography were carried out in a restricted part of Italy (Univ., Ferrara, 446) and in the Southern part of the Federal Republic of Germany (GSF, Neuherberg, 458). Special methodologies were developed for these surveys, so that the operators of the radiological units could carry out tests and measurements by themselves. It was found that procedures in mammography should be improved and consequently unnecessary exposures avoided, e.g. inadequate film processing was a main reason for dose variations. Mo-tubes with rotating anodes and film-screen combinations were recommended for better resolution and lower exposure; but unfortunately a proposed comparison between Mo- and W-tubes was not carried out (Univ., Ferrara, 446).

In the survey on dental radiological practices the entrance doses for the examination of a molar tooth showed variations by a factor of 12 (2.5 - 30 mGy). However, significant dose reduction were noted compared to surveys in 1970 and 1975 (GSF, Neuherberg, 458).

In France (CEPN, Fontenay-aux-Roses, 540) statistical data on dental practices and techniques used have been established. In this case skin doses were measured for various types of dental examinations and covered a range from 2.5 - 15 mGy.

2.2. Dose assement

Organ and tissue doses cannot easily be assessed because of the many factors which can influence the actual doses received by the patient. Various exposure conditions and patient parameters, such as sex, age, weight and dimensions must be taken into account. Direct and indirect measurements as well as calculations were carried out with a view to establish the necessary dose data. Various approaches were chosen for these assessments: e.g. surface doses were measured (Osp. S. Maria Mis., Udine, 516; Nuclear Energy Board, Dublin, 449) and the mean energy imparted to the patient was determined based on the exposure-area product (NRPB, Chilton, 387; Univ. Erlangen-Nürnberg, 368). In the latter the results agreed sufficiently with direct phantom measurements and the less time consuming dose assessment by means of the exposure-area product was preferred. Dose calculations have been improved by developing a complex inhomogeneous mathematical phantom (NRPB, Chilton, 387) and by introducing sex-specific male and female phantoms for a more accurate approach to real patients. Tables of conversion factors were set up, allowing the

calculation of doses for 40 organs using the technical parameters of typical radiographic techniques. Further studies are in progress to check if the data obtained by CT scanning could be used for better designing a three dimensional phantom (GSF, Neuherberg, 458).

A comparison of the methods used and the doses obtained has been started among this group of contractors with the aim of identifying the most appropriate methods for determing doses and improving the comparability of data. The outcome of this comparison action will pinpoint the areas in which exposure can be reduced and will support the definition of risk factors for the evaluation of the radiation detriment.

2.3. Dose reduction

Optimization of radiation protection in the medical use of ionizing radiation means optimization of the radiological procedure in order to obtain the clinical information at reasonably low doses and possibly at low costs. In practice substantial dose variations can be observed which exceed by a factor 2 or 3 the values obtained under optimal exposure conditions. Several research projects were set up to study the criteria for optimal image production, processing and interpretation procedures and to define the parameters for quality assurance and further dose reduction measures. The importance of optimal kV-values, of appropriate filtration and film-screen combination were stressed (Univ., Erlangen-Nürnberg, 368). The SLOT-technique, an alternative to antiscatter grids, proved, to be effective for contrast increase and dose reduction for special examinations (GSF, Neuherberg, 458).

The introduction of digital radiology may contribute to reduce patient exposure e.g. in ventriculography a 30 fold reduction has been obtained in comparison to conventional film techniques (Univ., Pisa, 373).

Thyroid and bone scintigraphy and cerebrovascular angiography have been tested for their diagnostic sensitivity and specificity in comparison to non radioactive methods. Bone scintigraphy can be recommended for the diagnosis of neoplastic bone diseases. In cerebrovascular angiography the criteria for admission for standard examination should be reviewed and made more stringent in order to avoid unnecesessary patient exposure (Univ., Pisa, 373).

Positron Emission Tomography (PET) gives new insights in regional biochemical organ functions, especially in neurological, cardiac and respiratory diseases including cancer and following aministration of drugs. High exposure inherent to this procedure could be reduced by working with more accurate and sensitive PET scanners. Equipment is available which offers at least a factor of 20 of improvement in sensitivity (MRC, London, 389).

Mass-screening practices in chest X-ray examinations have been studied in France (CEPN, Fontenay-aux-Roses, 423 - 002), and the Federal Republic of Germany (Univ., Erlangen-Nürnberg, 368) with a view to check their efficacy and efficiency as well as the doses delivered by the various equipments. The results have been presented at a workshop organized by the Commission and compared with the situation in the other Member States. It has been shown that doses could be reduced by selecting the appropriate equipment, e.g. refraining from photofluorographic cameras and using mainly full scale radiography combined with image intensifiers and rare-earth screens. It was emphasized that mass-screening actions should concentrate on population groups with a particular risk of pulmonary diseases.

3. PERSPECTIVES AND RECOMMENDATIONS

Statistical data on the situation and trends in diagnostic radiology, in patient exposure and dose reduction have been collected. Dose quantities describing population exposure such as the genetically significant dose, red bone marrow dose and effective dose equivalent have been assessed. Differences among those data for the various Member States remain to be explained. A consensus should be found about their usefulness for the description of risk factors.

From the variations of measured and calculated organ and tissue doses it became evident that standardization of procedures for dose assessment must be intensified. The necessity to introduce quality assurance of radiological techniques and processes is increasingly recognized. The analysis of the available data showed that for the establishment of detailed quality assurance programmes and for their implementation further research on specific criteria and their consequences on image quality and patient exposure is necessary.

Both the optimization of radiological procedures by quality assurance and dose reduction and the establishment of risk factors will back up the justification of the choice of certain radiological procedures for a given clinical indication.

Representative exposure conditions should be set up; they could support the standardization of radiological procedures and dose assessment methods so that comparable exposure data would become available. The elaboration of detailed quality assurance programmes and dose reduction measures would help the radiologist to obtain radiological images with less quality variations and better patient protection and could assist the manufacturers to design the radiological equipment considering both the requirement of the medical profession and low exposure to the patient. It is thus imperative that the results of these research efforts should be made known at a large scale.

PART 3. Management Aspects

The programme has been executed mainly by way of "cost-shared contracts" and, to a lesser extent, by the Biology Group at Ispra. During the four years between 1981 and 1984, the total budget for contracts amounted to 123 MioECU to which the Commission contributed 43.3 MioECU. Cost-sharing in contractual research, in which the Commission provides between 25% and 40% of the total budget of a research project, has proven to be an effective means for the execution of the Radiation Protection Research Programme: the projects are meeting the necessary national interest and priority to raise the complementary funds and the Commission can extend the programm to such a degree that contracts cover about 35% - 45% of all pertinent research in the Community. Nearly all relevant national institutions and universities are collaborating in the CEC programme; one may therefore estimate that in addition to the above mentioned contracts more than 80% of all radiation protection research is associated with the Radiation Protection Programme by way of scientific contacts, cooperation, information exchange, workshops etc. All these facts together thus multiply the influence of the money spent by the Commission by a factor of 6 to 8.

The organization of workshops, seminars, symposia, study groups and expert meetings by the Commission is considered as a indispensable complementary action that strengthens the impact of the programme and allows efficient coordination. During the 1981-1984 period 144 meetings were organized by the Commission (1) involving about 4.400 participants. In these meetings topical subjects were discussed, recent achievements were evaluated, scientific information, biological samples, methods, computer programmes etc. were exchanged and future research was planned. These meetings are excellent occasions for initiating practical cooperation between institutions or individuals. Assuming that about 1000 scientists are working fully or partially, in radiation protection research in the Community, and comparing this number with the participation at the meetings one can again see how the money spent by the programme has had an enhancing influence.

These meetings resulted in a number of proceedings which have been published. They are listed in Annex V together with other publications issued by the Commission (2) on topical questions of radiation protection making a total of 66.

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(1) For a complete list see Progress Report for 1981 and the following years.

(2) Directorate-General for Science, Research and Development (XII), Radiation Protection Programme,
Directorate-General Employment, Social Affairs and Education (V), Health and Safety Directorate.

Short-term study visits, and eventually even longer detachments, of scientists in other laboratories are possible within the frame of the contracts. Contractors made intensive use of this possibility for cooperation. Although no exact figures are available, one can estimate that more than 1000 short-term study visits between institutes from different countries took place. For financial reasons, the contractors had to limit the number of visits of scientists lasting 1 month or more, and about only a few longer detachments were feasible.

The Commission also provided 26 grants (1) equivalent to a total period of 720 months which allowed young scientists to undertake additional training in radiation protection research in laboratories of the Community.

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(1) Programme for the EAEC and the EEC in the field of special scientific and technical training, implemented by means of advanced training courses and grants, Council Decision of 17 March 1981.

PART 4. Annexes

ANNEX I

Members of the Advisory Committee on Programme Management
"BIOLOGY - HEALTH PROTECTION"
1981 - 1984

BELGIQUE - BELGIE

A. LAFONTAINE (Chairman 1984)
J. MAISIN
A. PRIEELS
O. VANDERBORGHT

BUNDESREPUBLIK DEUTSCHLAND

W. GOSSNER (Chairman 1982)
H.J. HARDT
A.M. KELLERER
J. MEHL
H. MUTH
E. OBERHAUSEN

DANMARK

M. FABER
H.L. GJOERUP
K.A. JESSEN
N.O. KJELDGAARD

ELLINIKI DIMOKRATIA

A. HADJIANTONIOU
E.G. SIDERIS

FRANCE

M. BERTIN
L. FITOUSSI
M. GRAS
H. JAMMET (Chairman 1981)

IRELAND

J.D. CUNNINGHAM
S.M. LAVELLE
A.W. MOORE
J. SCOTT

ITALIA

M. BELLI
A. CIGNA
G.F. CLEMENTE
L.V. POZZI

LUXEMBOURG

P. KAYSER

NEDERLAND

B. BOSNJAKOVIC
F.H. SOBELS
L. STRACKEE
D.W. van BEKKUM
G. WANSINK

UNITED KINGDOM

R.J. BERRY
J.A. DENNIS (Chairman 1983)
Sir Edward POCHIN
A.N.B. STOTT

COMMISSION

E. BENNETT
A.J. BERTINCHAMPS
F. VAN HOECK

H.G. EBERT (
J.M. MOUSNY (Secrétariat
H. SCHIBILLA (

ANNEX II

Members and participating experts
Management and Coordination Advisory Committee "RADIATION PROTECTION"
1985

BELGIQUE - BELGIE

P. DE SCHOUWER
A.M. PRIEELS
Experts : A. LAFONTAINE
P. LEJEUNE

BUNDESREPUBLIK DEUTSCHLAND

W. GOSSNER
H.J. HARDT
Expert : A.M. KELLERER

DANMARK

H.L. GJØRUP
N.O. KJELDGAARD (Chairman)
J. VISFELDT
Expert : K.A. JESSEN

ELLINIKI DIMOKRATIA

D. MAINTAS
E.G. SIDERIS

FRANCE

H. JAMMET
P. PELLERIN
Expert : M. GRAS

IRELAND

J.D. CUNNINGHAM
A.W. MOORE

ITALIA

A. CIGNA
F. MORSELLI
Expert : V. COVELLI

LUXEMBOURG

P. KAYSER

NEDERLAND

B. BOSNJAKOVIC
J. SCHNEIDER
Experts : M. FRISSEL
A.T. NATARAJAN
D.W. VAN BEKKUM

UNITED KINGDOM

R.J. COLE
E.D. RUBERY
Experts : R.J. BERRY
J.A. DENNIS
G. MEEKINGS
A.N.B. STOTT

COMMISSION

H. EBERT
H. ERISKAT

J.M. MOUSNY
H. SCHIBILLA : Secrétariat

ANNEX III

List of contracting laboratories, classified by sectors, who participated in the Radiation Protection Programme during the period 1981 - 1984

Head of research team	Institution/Place	Contract no
A. Radiation Dosimetry and its interpretation		
Barendsen, G.W.	TNO Rijswijk	BIO 300 NL
Blanc, D.	Univ. Toulouse	BIO 295 F
Blanc, D./Teyssier, J.L.	Univ. Toulouse	BIO 296 F
Broerse, J.J.	TNO Rijswijk	BIO 302 NL
Broerse, J.J.	TNO Rijswijk	BIO 525 NL
Christmas, P.	NPL Teddington	BIO 307 UK
Christmas, P.	NPL Teddington	BIO 506 UK
de Choudens, H.	CEA, CEN Grenoble	BIO 293 F
de Choudens, H.	CEA, CEN Grenoble	BIO 523 F
Enderby, J.E.	Univ. Bristol	BIO 564 UK
Feinendegen, L.E.	KFA Jülich	BIO 288 D
Jackson, D.F.	Univ. Guildford	BIO 526 UK
Jacobi, W.	GSF Neuherberg	BIO 563 D
Jacobi, W./Burger, G.	GSF Neuherberg	BIO 287 D
Jahr, R.	PTB Braunschweig	BIO 291 D
Jahr, R.	PTB Braunschweig	BIO 502 D
Jahr, R./Reich, H.	PTB Braunschweig	BIO 284 D
Kellerer, A.M.	Univ. Würzburg	BIO 286 D
Mallard, J.R./Ettinger, K.V.	Univ. Aberdeen	BIO 310 UK
Marshall, T.O.	NRPB Chilton	BIO 308 UK
Martin, H./Watt, D.E.	Univ. Dundee	BIO 463 UK
McKinlay, A.	NRPB Chilton	BIO 309 UK
Metalli, P.	ENEA, CSN Casaccia	BIO 298 I
Metalli, P./Tommasino, L.	ENEA, CSN Casaccia	BIO 299 I
Moschini, G.	Ist. Fis. Nucl. Legnaro	BIO 297 I
Müller, K.D.	KFA Jülich	BIO 504 D
Muth, H./Grillmaier, R.E.	Univ. Homburg	BIO 289 D
Muth, H./Menzel, H.G.	Univ. Homburg	BIO 482 D
Newton, D./Leake, J.W.	UKAEA Harwell	BIO 434 UK
Parmentier, N.	CEA, CEN Fontenay-aux-Roses	BIO 433 F
Peirson, D.H.	UKAEA Harwell	BIO 305 UK
Peirson, D.H.	UKAEA Harwell	BIO 306 UK
Peirson, D.H.	UKAEA Harwell	BIO 459 UK
Portal, G.	CEA, CEN Fontenay-aux-Roses	BIO 292 F
Portal, G.	CEA, CEN Fontenay-aux-Roses	BIO 483 F
Portal, G.	CEA, CEN Fontenay-aux-Roses	BIO 505 F
Portal, G.	CEA, CEN Fontenay-aux-Roses	BIO 522 F
Portal, G.	CEA, CEN Fontenay-aux-Roses	BIO 543 F
Rachenmann, R.V.	Univ. Strasbourg	BIO 294 F
Scharmann, A.	Univ. Giessen	BIO 503 D
Simoen, J.P.	CEA, CEN Saclay	BIO 524 F
Weller, B.E.	Polytech. South Bank London	BIO 544 UK
CENDOS	TNO Rijswijk	BIO 311 NL
EURADOS	TNO Rijswijk	BIO 507 NL
ICRU	Bethesda	BIO 312 US

B. Behaviour and control of radionuclides in the environment

Aarkrog, A.	RISØ Nat. Lab. Roskilde	BIO 339	DK
Allen, S.E.	Nat. Env. Res. C. Swindon	BIO 439	UK
BÄchmann, K.	Tech. Hochschule Darmstadt	BIO 487	D
Baudin, G.	CEA, CEN Fontenay-aux-Roses	BIO 465	F
Belot, Y.	CEA, CEN Fontenay-aux-Roses	BIO 340	F
Busuoli, G.	ENEA Bologna	BIO 324	I
Caput, C.	CEA, CEN Fontenay-aux-Roses	BIO 466	F
Chalabreysse, J.	CEA, CEN Pierrelatte	BIO 508	F
Charalambous, S./Papastefanou,C.	Univ. Thessaloniki	BIO 533	GR
Cigna, A.	ENEA, CSN Casaccia	BIO 322	I
Cinelli, F.	Cent. Bio. Mar. Livorno	BIO 519	I
Clemente, G.F.	ENEA, CSN Casaccia	BIO 323	I
Cremers, A.	KUL Leuven	BIO 531	B
Duursma, E.K./Frissel, M.J./ Martin, J.M.	Delta Inst. Yerseke/ ITAL Wageningen/ENS Paris	BIO 326	NL
Fontaine, R.	CEA, CEN Fontenay-aux-Roses	BIO 464	F
Frissel, M.J.	RIVM-ITAL Wageningen	BIO 325	NL
Grauby, A.	CEA, CEN Cadarache	BIO 317	F
Grauby, A.	CEA, CEN Cadarache	BIO 318	F
Grauby, A.	CEA, CEN Cadarache	BIO 528	F
Grauby, A.	CEA, CEN Cadarache	BIO 529	F
Grauby, A.	CEA, CEN Cadarache	BIO 530	F
Grauby, A./Picat, Ph.	CEA, CEN Cadarache	BIO 321	F
Grauby, A./Saas, A.	CEA, CEN Cadarache	BIO 315	F
Guegueniat, P.	CEA, CEN La Hague	BIO 316	F
Hamilton, E.I.	Nat.Env.Res.C. Swindon	BIO 438	UK
Hoppenheit, M.	Bio. Anst. Helgol. Hamburg	BIO 559	D
Janssens, A.	Rijksuniv. Gent	BIO 327	B
Kaul, A./Kistner, G.N.	BGA Neuherberg	BIO 313	D
Kiefer, H.	KFZ Karlsruhe	BIO 484	D
Kirchmann, R.	CEN, SCK Mol	BIO 431	B
Kirchmann, R.	CEN, SCK Mol	BIO 467	B
KÜhn, W.	GSF Hannover	BIO 314	D
Laudelout, H.	Univ. Louvain-la-Neuve	BIO 328	B
Madelaine, G.	CEA, CEN Fontenay-aux-Roses	BIO 436	F
Maisin, J.R.	CEN, SCK Mol	BIO 330	B
McAulay, I.R.	Univ. Dublin	BIO 338	EIR
McAulay, I.R.	Univ. Dublin	BIO 562	EIR
Mitchell, N.T./Pentreath, R.J.	MAFF. Lowestoft	BIO 331	UK
Morgan, A.	UKAEA Harwell	BIO 334	UK
Morgan, A.	UKAEA Harwell	BIO 561	UK
Nielsen, N.E.	Univ. Copenhagen	BIO 486	DK
O'Riordan, M.C.	NRPB Chilton	BIO 545	UK
O'Riordan, M.C.	NRPB Chilton	BIO 546	UK
Peirson, D.H.	UKAEA Harwell	BIO 332	UK
Peirson, D.H.	UKAEA Harwell	BIO 333	UK
Pieri, J.	Univ. Nantes	BIO 435	F
Pieri, J.	Univ. Nantes	BIO 527	F
Postma, H.	NIOZ Den Burg	BIO 509	NL
Smith, H.	NRPB Chilton	BIO 336	UK
Smith, H.	NRPB Chilton	BIO 521	UK
Steffens, W.	KFA Jülich	BIO 560	D

van den Hoek, J.	Landbouwh. Wageningen	BIO 432 NL
Van der Ben, D.	IRSNB Bruxelles	BIO 485 B
Vanderborght, O.	SCK, CEN Mol	BIO 329 B
IUR	Oupeye	BIO 468 B
IUR	Oupeye	BIO 534 B

C. Short-term somatic effects of ionizing radiation

Adams, G.E./Fielden, E.M.	MRC Harwell	BIO 363 UK
Apelgot, S.	Inst. Curie Paris	BIO 349 F
Cramp, W.A.	MRC London	BIO 361 UK
Errera, M.	Univ. Bruxelles	BIO 359 B
Hagen, U.	GSF Neuherberg	BIO 343 D
Hüttermann, J./Müller-Broich, A.	Univ. Regensburg	BIO 342 D
Köhnlein, W.	Univ. Münster	BIO 470 D
Loman, H.	Univ. Amsterdam	BIO 356 NL
Quintiliani, M.	ENEA, CNR Casaccia	BIO 441 I
Schnabel, W.	HMI Berlin	BIO 469 D
Schulte-Frohlinde, D./ von Sonntag, C.	MPI Mülheim	BIO 341 D
Symons, M.C.R.	Univ. Leicester	BIO 362 UK
Têoule, R./Cadet, J.	CEA, CEN Grenoble	BIO 350 F
Bazin, H.	Univ. Louvain-la-Neuve	BIO 358 B
Bazin, H.	Univ. Louvain-la-Neuve	BIO 512 B
Courtois, Y.	INSERM Paris	BIO 351 F
Daburon, F.	CEA, CEN Saclay	BIO 347 F
Doria, G.	ENEA, CSN Casaccia	BIO 354 I
Dumont, J.E.	Univ. Bruxelles	BIO 360 B
Emerit, I.	Univ. Paris	BIO 510 F
Fliedner, T.M.	Univ. Ulm	BIO 345 D
Funck-Brentano, J.L.	INSERM Paris	BIO 511 F
Garattini, S./Spreafico, F.	Ist. M. Negri Milano	BIO 355 I
Greally, J./Kennedy, J.D.	Univ. College Galway	BIO 443 EIR
Jammet, H.	Inst. Curie Paris	BIO 348 F
Jonker, M.	TNO Rijswijk	BIO 535 NL
Kaul, A.	BGA Neuherberg	BIO 518 D
Lafuma, J.	CEA, CEN Fontenay-aux-Roses	BIO 346 F
Macieira-Coelho, A.	Assoc. C. Bernard Paris	BIO 352 F
Peckham, M.J./Adams, G.E.	RMH Sutton	BIO 488 UK
Peschle, C.	Univ. Napoli	BIO 353 I
Streffer, C.	Univ. Essen	BIO 290 D
Taaffe, J.K./Malone, J.F.	Coll. of Technol. Dublin	BIO 364 EIR
Thierfelder, S.	GSF München	BIO 344 D
Tipton, K.F.	Trinity College Dublin	BIO 494 EIR
van Bekkum, D.W.	TNO Rijswijk	BIO 357 NL
IBMTR	Wisconsin	BIO 471 US
IBMTR	Wisconsin	BIO 520 US

D. Late somatic effects of ionizing radiation

Adams, G.E./Cobb, L.M.	MRC Harwell	BIO 384 UK
Adams, G.E./Hulse, E.V.	MRC Harwell	BIO 385 UK
Bentvelzen, P.A.J.	TNO Rijswijk	BIO 376 NL
Broerse, J.J.	TNO Rijswijk	BIO 375 NL
Chalabreysse, J.	CEA, CEN Pierrelatte	BIO 372 F
Chapman, B.G./Ramsden, D.	UKAEA Winfrith	BIO 380 UK
Duplan, J.F.	Fond. Bergonie Bordeaux	BIO 371 F
Field, S.B.	MRC London	BIO 474 UK
Gössner, W.	GSF Neuherberg	BIO 366 D
Gössner, W./Kellerer, A.M./ Spiess, H.	GSF Neuherberg/Univ. Würzburg/Univ. München	BIO 461 D
Hogeweg, B./Barendsen, G.W.	TNO Rijswijk	BIO 301 NL
Hollander, C.F./Broerse, J.J.	TNO Rijswijk	BIO 567 NL
Hopewell, J.W.	Univ. Oxford	BIO 382 UK
Hopewell, J.W.	Univ. Oxford	BIO 490 UK
Hornsey, S.	MRC London	BIO 442 UK
Kjeldgaard, N.O.	Univ. Aarhus	BIO 547 DK
Kriegel, H.	GSF Neuherberg	BIO 365 D
Lafuma, J.	CEA, CEN Fontenay-aux-Roses	BIO 370 F
Lambert, B.E./Coggle, J.E.	St Barthol. Hosp. London	BIO 383 UK
Maisin, J.R.	CEN, SCK Mol	BIO 378 B
Maisin, J.R.	CEN, SCK Mol	BIO 379 B
Maisin, J.R.	CEN, SCK Mol	BIO 492 B
Masse, R.	CEA, IPSN Fontenay-aux-Roses	BIO 565 F
Morgan, A.	UKAEA Harwell	BIO 386 UK
Morgan, A.	UKAEA Harwell	BIO 448 UK
Morgan, A.	UKAEA Harwell	BIO 568 UK
Simmons, J.A.	PCL London	BIO 381 UK
Smith, H.	NRPB Chilton	BIO 388 UK
Smith, H.	NRPB Chilton	BIO 489 UK
Tallone-Lombardi, L.	Univ. Milano	BIO 552 I
Taylor, D.M.	KFZ Karlsruhe	BIO 367 D
Vanderborght, O.	SCK, CEN Mol	BIO 377 B
Vanderborght, O.	SCK, CEN Mol	BIO 566 B
van Putten, L.M.	TNO Rijswijk	BIO 374 NL
Williams, E.D.	Welsh Nat. Sch. Med. Cardiff	BIO 569 UK
EULEP	Bordeaux	BIO 390 D
EULEP	Bordeaux	BIO 491 D

E. Genetic effects of ionizing radiation

Adams, G.E.	MRC Harwell	BIO 412 UK
Adams, G.E./Cattanach, B.M.	MRC Harwell	BIO 453 UK
Adams, G.E./Cattanach, B.M.	MRC Harwell	BIO 457 UK
Adams, G.E./Savage, J.R.K.	MRC Harwell	BIO 454 UK
Adams, G.E./Searle, A.G.	MRC Harwell	BIO 452 UK
Altland, K.	Univ. Giessen	BIO 550 D
Bootsma, D.	Univ. Rotterdam	BIO 404 NL
Bridges, B.A.	MRC Brighton	BIO 414 UK
Brodthagen, H.	Finseninst. København	BIO 455 DK
Celis, J.E.	Univ. Aarhus	BIO 416 DK
Cohn, P./Holt, G.	PCL London	BIO 479 UK
Dalebroux, M.	INRA Dijon	BIO 419 F
de Boer, P.	Landbouwh. Wageningen	BIO 402 NL
Delpoux, M.	Univ. Toulouse	BIO 430 F
Devoret, R.	CNRS Gif-sur-Yvette	BIO 426 F
Dutrillaux, B.	Inst. Progenèse Paris	BIO 398 F
Ehling, U.H.	GSF Neuherberg	BIO 395 D
Ehling, U.H.	GSF Neuherberg	BIO 549 D
Evans, H.J.	WGH/MRC Edinburgh	BIO 493 UK
Falaschi, A./Bertazzoni, U.	Univ. Pavia	BIO 428 I
Falaschi, A./Bertazzoni, U.	Univ. Pavia	BIO 553 I
Farulla, A.	ENEL Roma	BIO 401 I
Goffeau, A.	Univ. Louvain-la-Neuve	BIO 410 B
Göhde, W.	Univ. Münster	BIO 538 D
Hansmann, I.	Univ. Göttingen	BIO 393 D
Harder, D.	Univ. Göttingen	BIO 570 D
Houghton, J.A.	Univ. Galway	BIO 415 EIR
Houghton, J.A.	Univ. Galway	BIO 514 EIR
Jung, H.	Univ. Hamburg	BIO 391 D
Kiefer, J.	Univ. Giessen	BIO 392 D
Leenhouts, H.P.	ITAL Wageningen	BIO 409 NL
Leenhouts, H.P.	ITAL Wageningen	BIO 478 NL
Léonard, A.	CEN, SCK Mol	BIO 451 B
Lohman, P.H.M.	TNO Rijswijk	BIO 403 NL
Moustacchi, E.	Inst. Curie Orsay	BIO 397 F
Natarajan, A.T.	Univ. Leiden	BIO 421 NL
Nicoletti, B.	Univ. Roma	BIO 475 I
Olivieri, G.	Univ. Roma	BIO 400 I
Olivieri, G.	Univ. Roma	BIO 450 I
Parry, J.M.	Univ. Swansea	BIO 411 UK
Peirson, D.H.	UKAEA Harwell	BIO 460 UK
Pohlit, W.	GSF Frankfurt	BIO 394 D
Pohlit, W.	GSF Frankfurt	BIO 513 D
Radman, M.	Univ. Bruxelles	BIO 420 B
Radman, M.	Univ. Bruxelles	BIO 548 B
Sarasin, A.	Inst. RSC Villejuif	BIO 427 F
Sarasin, A.	Inst. RSC Villejuif	BIO 551 F
Searle, A.G.	MRC Harwell	BIO 429 UK
Simons, J.W.I.M.	Univ. Leiden	BIO 407 NL
Smith, H.	NRPB Chilton	BIO 413 UK
Sobels, F.H.	Univ. Leiden	BIO 406 NL
Starlinger, P.	Univ. Köln	BIO 396 D
Strom, R.	Univ. Roma	BIO 399 I
Sybenga, J.	Landbouwh. Wageningen	BIO 477 NL

van de Putte, P.	Univ. Leiden	BIO 408 NL
van der Eb, A.J.	Univ. Leiden	BIO 405 NL
van der Eb, A.J.	Univ. Leiden	BIO 476 NL
von Wettstein, D.	Carlsb. Lab. København	BIO 417 DK
Westergaard, O./Nielsen, O.F.	Univ. Aarhus	BIO 418 DK
CEC-Biology Group	Ispra **	

F. Evaluation of radiation risks

Bagni, B./Rimondi, O.	Univ. Ferrara	BIO 446 I
Barbina, V.	Osp. S. Maria Mis. Udine	BIO 516 I
Cunningham, J.D.	Nucl.Ener.Board Dublin	BIO 449 EIR
Donato, L.	Univ. Pisa	BIO 373 I
Fagnani, F.	CEPN Fontenay-aux-Roses	BIO 540 F
Jacobi, W./ Drexler, G.	GSF Neuherberg	BIO 458 D
Jones, T.	MRC London	BIO 389 UK
McKinlay, A.	NRPB Chilton	BIO 387 UK
McKinlay, A.	NRPB Chilton	BIO 497 UK
Pauly, H.	Univ. Erlangen	BIO 368 D
Bazzano, E.	CISE Segrate	BIO 495 I
Clemente, G.F.	ENEA, CSN Casaccia	BIO 480 I
Coulon, R.	CEDHYS Fontenay-aux-Roses	BIO 320 F
Fagnani, F.	CEPN Fontenay-aux-Roses	BIO 444 F
Gjørup, H.L.	RISØ Nat. Lab. Roskilde	BIO 555 DK
Goddard, A.J.H.	ICST London	BIO 571 UK
Goddard, A.J.H./Bell, J.N.B.	ICST London	BIO 499 UK
Hémon, D.	INSERM Villejuif	BIO 445 F
Hémon, D.	INSERM Villejuif	BIO 515 F
Hill, M.D./Linsley, G.S.	NRPB Chilton	BIO 424 UK
Hill, M.D./Linsley, G.S.	NRPB Chilton	BIO 542 UK
Jacobi, W./Paretzke, H.G.	GSF Neuherberg	BIO 422 D
Janssens, A.	Univ. Gent	BIO 496 B
Knox, E.G.	Univ. Birmingham	BIO 541 UK
Kollas, J.	NRC Democritos Athens	BIO 557 GR
McKinlay, A.	NRPB Chilton	BIO 335 UK
McKinlay, A.	NRPB Chilton	BIO 337 UK
McKinlay, A.	NRPB Chilton	BIO 500 UK
McKinlay, A.	NRPB Chilton	BIO 501 UK
McKinlay, A.	NRPB Chilton	BIO 573 UK
McLaughlin, J.P./McAulay, I.R.	Univ. College Dublin	BIO 517 EIR

** Biology Group of the Commission of the European Communities DG XII, Biology, Radiation Protection and Medical Research, at the Ispra Establishment of the Joint Research Centre.

Nenot, J.C.	CEA, CEN Fontenay-aux-Roses	BIO 319 F
O'Riordan, M.C.	NRPB Chilton	BIO 556 UK
O'Riordan, M.C./McKinlay, A.	NRPB Chilton	BIO 498 UK
Rininsland, H.	KFZ Karlsruhe	BIO 539 D
Scheer, K.E.	DKFZ Heidelberg	BIO 369 D
Uzzan, G.	CEA, CEN Fontenay-aux-Roses	BIO 423 F
Sub-contracts :		
Goddard, A.J.H.	ICST London	SC 001 UK
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 002 F
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 003 F
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 004 F
Pagès, J.P.	LSEES Fontenay-aux-Roses	SC 005 F
Pagès, J.P.	LSEES Fontenay-aux-Roses	SC 006 F
Chalabreysse, J.	CEA, CEN Grenoble	SC 007 F
Dean, G.	MSRB Dublin	SC 008 EIR
Dean, G.	MSRB Dublin	SC 009 EIR
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 010 F
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 011 F
Nihoul, J.C.	Univ. Liège	SC 012 B
Guegueniat, P.	CEA, CEN La Hague	SC 013 F
Gjørup, H.L.	RISØ Nat. Lab. Roskilde	SC 014 DK
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 015 F
Dean, G.	MSRB Dublin	SC 016 EIR
Cartan, V.L.	EPFP Sceaux	SC 017 F
Delpoux, M.	Univ. Toulouse	SC 018 F
Lacourly, G.	Orsay	SC 019 F
Fagnani, F.	CEPN Fontenay-aux-Roses	SC 020 F
Gillessen,	IABG Ottobrunn	SC 021 D
Ericson, S.O.	AIB Solna	SC 022 S
Benco, A.	JRC Ispra	SC 023 I
Wheatley, B.M.	CEGB Berkeley	BIO 572 UK
Zettwoog, P.	CEN Fontenay-aux-Roses	BIO 554 F
ICRP	Surrey	BIO 425 UK

ANNEX IV

Geographical distribution of contracts
(Number of contracts)

BELGIQUE / BELGIE

Bruxelles/Brussel
IRSNB 1
ULB 4

Gent
Rijksuniv. 2

Leuven
KUL 1

Liège
Univ. 1

Louvain-la-Neuve
UCL 4

Mol
CEN/SCK 10

DANMARK

Aarhus
Univ. 3

Copenhagen
Carlsb. Lab. 1
Finsen Inst. 1
Univ. 1

Roskilde
Risø Nat. Lab. 3

BUNDESREPUBLIK DEUTSCHLAND

Berlin
HMI 1

Braunschweig
PTB 3

Darmstadt
Tech. Hochsch. 1

Erlangen
Univ. 1

Essen
Univ. 1

Frankfurt
GSF 2

Giessen
Univ. 3

Göttingen
Univ. 2

Hamburg
Univ. 1
Bio. Anst. Helgoland 1

Hannover
GSF 1

Heidelberg
DKFZ 1

Homburg
Univ. 2

Jülich
KFA 3

Karlsruhe
KFZ 3

Köln
Univ. 1

Mülheim
MPI 1

München
GSF 1
Univ. 1

Münster
Univ. 2

Neuherberg
BGA 2
GSF 10

Ottobrunn
IABG 1

Regensburg
Univ. 1

Ulm
Univ. 1

Würzburg
Univ. 2

ELLINIKI DIMOKRATIA

Athens
NRC 1

Thessaloniki
Univ. 1

FRANCE

Bordeaux
Fond. Bergonie 1

Cadarache
CEA 7

Dijon
INRA 1

Fontenay-aux-Roses
CEA 15
CEDHYS 1
CEPN 9
IPSN 1
LSEES 2
STEP 1

Gif-sur-Yvette
CNRS 1

Grenoble
CEA 4

La Hague
CEA 2

Nantes
Univ. 2

Orsay
Inst. Curie 1

Paris
Ass. Cl. Bernard 1
Ec. Norm. Sup. 1
INSERM 2
Inst. Curie 2
Inst. Progen. 1
Univ. 1

Pierrelatte
CEA 2

Saclay
CEA 2

Sceaux
EPFP 1

Strasbourg
Univ. 1

Toulouse
Univ. 4

Villejuif
INSERM 2
Inst. RSC 2

IRELAND

Dublin
Coll. Techn. 1
MSRB 3
Nucl. Energy Board 1
Univ. 4

Galway
Univ. 3

ITALIA

Bologna
ENEA 1

Casaccia
ENEA 7

Ferrara
Univ. 1

Ispra
Biol. Group CEC 1
JRC 1

Legnaro
Ist. Fis. Nucl. 1

Livorno
Cent. Biol. Mar. 1

Milano
Ist. M. Negri 1
Univ. 1

Napoli
Univ. 1

Pavia
Univ. 2

Pisa
Univ. 1

Roma
ENEL 1
Univ. 4

Segrate
CISE 1

Udine
Osped. 1

NEDERLAND

Amsterdam
Univ. 1

Den Burg
Nioz 1

Leiden
Univ. 6

Rijswijk
TNO 11

Rotterdam
Univ. 1

Wageningen
RIVM-ITAL 4
Landbouwh. 3

Yerseke
Delta Inst. 1

SWEDEN

Solna
AIB 1

UNITED KINGDOM

Aberdeen
Univ. 1

Berkeley
BNL 1

Birmingham
Univ. 1

Brighton
MRC 1

Bristol
Univ. 1

Cardiff
Welsh Nat. School 1

Chilton
NRPB 20

Dundee
Univ. 1

Edinburgh
MRC 1

Guildford
Univ. 1

Harwell
MRC 8
UKAEA 13

Leicester
Univ. 1

London
Imp. Coll. 3
MRC 5
PCL 3
Poly. South Bank 1
St. Barthol. Hosp. 3

Lowestoft
MAFF 1

Oxford
Univ. 2

Sutton
ICR 1
RMH 1

Swansea
Univ. 1

Swindon
NERC 2

Teddington
NPL 2

Winfrith
UKAEA 1

GROUP CONTRACTS and OTHERS

CENDOS 1
EULEP 2
EURADOS 1
IBMTR 2
ICRP 1
ICRU 1
IUR 2

ANNEX V

LIST OF PROCEEDINGS OF SCIENTIFIC MEETINGS(1) AND OTHER PUBLICATIONS ON RADIATION PROTECTION

- Radiation Protection Programme 1980-1984 - Research priorities and Scientific Documentation

  Document N° XII/1067/79, 1979, 345 pages

- Council Directive of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation

  Report EUR 7330, 1981, 74 pages

- Progress Report of the Radiation Protection Programme 1976-1980 (Final Report)

  Report EUR 7169, 1981, 1342 pages

- Radiation protection optimization: present experience and methods

  Proceedings of a seminar, Luxembourg, 3-5 October 1979
  edited by H.G. EBERT, H. ERISKAT, A. OUDIZ, G. UZZAN
  Report EUR 7001, Pergamon Press Ltd., 1981, 322 pages

- Techniques for identifying transuranics specification in the aquatic environments

  Proceedings of a technical committee meeting, Ispra, 24-28 March 1980
  IAEA-Panel Proceedings Series, 1981, 293 pages

- Pathogenesis of microbial infections after radiation injury

  Monograph by H. BAZIN
  Report EUR 6671, 1981, 135 pages

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(1) Workshops, Seminars or Symposia organized, co-organized or co-sponsored by the Commission of the European Communities

- Plutonium in freshwater ecosystems: a literature review

  Monograph by M. METAYER-PIRET, G.B. GERBER, L. FOULQUIER
  European Appl. Res. Reports, Vol. 1, Nr. 3, 1981, pp. 417-490

- Agricultural measures to reduce radiation doses to man caused by severe nuclear accidents

  Monograph by F. VAN DORP, R. ELEVELD, M.J. FRISSEL
  Report EUR 7370, 1981, 112 pages

- Bone and bone-seeking radionuclides: physiology, dosimetry and effects

  Proceedings of a symposium, Rotterdam, 29 August 1980
  edited by V. VOLF
  Report EUR 7168, Harwood Acad. Publ. 1981, 153 pages

- 7th Symposium on Microdosimetry

  Proceedings of the Symposium, Oxford, 8-12 September 1980
  edited by J. BOOZ, H.G. EBERT, H.D. HARTFIEL
  Report EUR 7147, Harwood Acad. Publ. 1981, Vol. I + II: 1.586 pages

- Radiation protection quantities for external exposure

  Proceedings of a seminar, Braunschweig, 13-15 October 1980
  edited by G. BURGER, H.G. EBERT, D. HARDER, R. KRAMER, S. WAGNER
  Report EUR 7101, Harwood Acad. Publ. 1981, 260 pages

- Patient exposure to radiation in medical X-ray diagnosis - possibilities for dose reduction

  Proceedings of a seminar, Neuherberg, 27-30 April 1981
  edited by G. DREXLER, H. ERISKAT, H. SCHIBILLA
  Report EUR 7438, 1981, 470 pages

- 4th Symposium on Neutron Dosimetry

  Proceedings of the Symposium, Neuherberg, 1-5 June, 1981
  edited by G. BURGER, H.G. EBERT
  Report EUR 7448, 1981, Vol. I + II: 1.311 pages

- The molecular theory of radiation biology

  Monograph by K.H. CHADWICK, H.P. LEENHOUTS
  Monographs on Theoretical and Applied Genetics, Vol. 5, Springer Verlag, 1981, 377 pages

- Assessment of plutonium internal contamination in man

  G.F. CLEMENTE, A. DELLE SITE
  Report EUR 7157, 1981, 183 pages

- 3rd Seminar on The radiation protection dosemeter intercomparison programme - beta incomparison

  Proceedings of the Seminar, Grenoble, 6-8 October 1980
  Report EUR 7365, 1981, 210 pages

- Radiation Protection Programme 1980-1984 - Catalogue of Contracts

  Document N° XII/466/82, 1982, Vol. I + II: 605 pages

  Addendum I: Document N° XII/1078/83, 1983, Vol. I + II: 225 pages

  Addendum II:Document N° XII/625/85, 1985, Vol. I + II: 135 pages

- Radiation Protection Programme 1976-1980 - Synthesis of Results

  Document N° XII/340/82, 1982, 175 pages

- Progress Report of the Radiation Protection Programme 1981

  Report EUR 7800, 1982, 1069 pages

- Genetic effects of ionizing radiations in multicellular eukaryotes and the assessment of genetic radiation hazards in man

  Monograph by K. SANKARANARAYANAN
  Elsevier Biomedical Press, 1982, 385 pages

- Cytogenetic response in vivo to ionizing radiations in somatic and germ cells of mammals including man

  Abstracts from a contractors' meeting, Brussels, 27-28 October 1981
  Mutation Research 95, 1982, pp. 1-77

- Biochemistry and genetics of sensitivity and repair of DNA

  Abstracts from a contractors' meeting, Giessen, 5-6 October 1981
  Mutation Research 96, 1982, pp. 119-151

- Late effects after therapeutic whole body irradiation

  Proceedings of a symposium, München, 27-28 August 1981
  edited by T.M. FLIEDNER, W. GOSSNER, G. PATRICK
  Report EUR 8070, 1982, 139 pages

- Neutron carcinogenesis

  Proceedings of a seminar, Rijswijk, 30 March - 1 April 1982
  edited by J. BROERSE and G.B. GERBER
  Report EUR 8084, 1982, 455 pages

- Results of environmental radioactivity measurements in the Member States of the European Community for air - deposition - water - milk, 1980

  20th report
  Report EUR 7639, 1982

- Operational quantities for use in external radiation protection measurements - An investigation of concepts and principles

  Report EUR 8346, 1982, 40 pages

- Methods of evaluation of the consequences of irradiation of the population

  edited by Commissariat à l'Energie Atomique and CEC
  Report EUR 8068, 1982, 450 pages

- Problems of applying the Directive laying down the Euratom basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation

  Proceedings of a seminar, Luxembourg, 4-5 June 1981
  Report EUR 8287, 1982, 141 pages

- Progress Report of the Radiation Protection Programme 1982

  Report EUR 8486, 1983, 1225 pages

- 8th Symposium on Microdosimetry

  Proceedings of the Symposium, Jülich, 27 September - 1 October 1982
  edited by J. BOOZ, H.G. EBERT
  Report EUR 8395, 1983, 1221 pages

- Transfer of radioactive materials in the terrestrial environment subsequent to an accident release to atmosphere

  Proceedings of a seminar, Dublin, 11-15 April 1983
  Document N° V/3004/83, 1983, Vol. I + II: 728 pages

- Radiobiology of radium and the actinides in man,

  Proceedings of a conference, Lake Geneva, 11-16 October 1981
  edited by J. RUNDO, P. FAILLA, R.A. SCHLENKER, G.J. HAMILTON
  Health Physics 44, Supplement N° 1, 1983, 589 pages

- Results of a quality assurance exercice for radon and radon decay product measurements

  Intercomparison report
  Report EUR 8629, 1983, 55 pages

- Radioactive effluents from nuclear power stations and nuclear fuel reprocessing plants in the E.C.; discharge data 1976-1980, radiological aspects

  F. LUYKX, G. FRASER
  Document N° V/3267/83, 1983, 70 pages

- Results of environmental radioactivity measurements in the Member States of the European Community for air - deposition - water - milk - 1981

  21st report
  Report EUR 8308, 1983, 287 pages

- Environmental monitoring - European interlaboratory test programme for integrating dosemeter systems

  E. PIESCH, B. BURGKHARDT
  Report EUR 8932, 1983, 125 pages

- Iodine filters in nuclear installations

  J.G. WILHELM
  Document N° V/2110/83, 1983, 219 pages

- Radionuclide distribution and transport in terrestrial and aquatic ecosystems

  P.J. COUGHTREY, M.C. THORNE, D. JACKSON
  A.A. BALKEMA Publishers, 1983, Vol. I + II + III: 1.408 pages

- Progress Report of the Radiation Protection Programme 1983

  Report EUR 9088, 1984, 1353 pages

- Evaluation of the European Community's Radiation Protection Programme 1976-1980

  W.K. SINCLAIR, R.L. AKEHURST, G. BRESSON, E. OBERHAUSEN, P. OFTEDAL, G. SILINI, A. WAMBERSIE

  Report EUR 8648, 1984, 156 pages

- The German thorotrast study; results of epidemiological, clinical and biophysical examinations on radiation-induced late effects in man caused by incorporated colloidal thorium dioxide (thorotrast)

  Monograph by G. VAN KAICK, H. MUTH, A. KAUL
  Report EUR 9504, 1984, 244 pages

- Atmospheric transport of radioisotopes and the assessment of population doses on a European scale; application of the MESOS code to the meteorological dispersion of radioactive discharges from national nuclear sites in the European Community with particular reference to the mesoscale

  Monograph by H.M. APSIMON, A.J.H. GODDARD
  Report EUR 9128, 1984, 463 pages

- Effects of prenatal irradiation with special emphasis on late effects

  Proceedings of a symposium, Bordeaux, 29 July 1982
  edited by C. STREFFER, G. PATRICK
  Report EUR 8067, 1984, 242 pages

- Risks from Tritium exposure

  Proceedings of a seminar, Mol, 22-24 November 1982
  edited by G.B. GERBER, C. MYTTENAERE
  Report EUR 9065, 1984, 351 pages

- Behaviour of long-lived radionuclides in the marine environment

  Proceedings of a symposium, La Spezia, 28-30 September 1983
  Report EUR 9214, 1984, 463 pages

- Indoor exposure to natural radiation and related risk assessment

  Proceedings of a seminar, Anacapri, 3-5 October 1983
  edited by G.F. CLEMENTE, H. ERISKAT, M.C. O'RIORDAN, J. SINNAEVE
  Radiation Protection Dosimetry, Vol. 7, N° 1-4, 1984, 439 pages

- Environmental transfer to man of radionuclides released from nuclear installations

  Proceedings of a seminar, Brussels, 17-21 October 1983
  Document N° V/7400/84, 1984, Vol. I+II: 909 pages

- 2nd Seminar on Radiation protection optimization "AS LOW AS REASONABLY ACHIEVABLE",....

  Proceedings of the Seminar, Luxembourg, 8-9 November 1983
  edited by A. JOLIVET, J. SINNAEVE
  Report EUR 9173, 1984, 515 pages

- Lung modelling for inhalation of radioactive materials

  Proceedings of a workshop, Oxford, 26-28 March 1984
  edited by H. SMITH, G.B. GERBER
  Report EUR 9384, 1984, 340 pages

- Role of microorganisms on the behaviour of radionuclides in aquatic and terrestrial systems and their transfer to man

  Proceedings of a workshop, Brussels, 25-27 April 1984
  edited by E. BONNYNS-VAN GELDER, R. KIRCHMANN
  Report IUR/CEC, 1984, 285 pages

- Microdosimetric counters in radiation protection

  Proceedings of a workshop, Homburg/Saar, 15-17 May 1984
  edited by J. BOOZ, A.A. EDWARDS, K.G. HARRISON
  Radiation Protection Dosimetry, Vol. 9, N° 3, 1984, 253 pages

- Radionuclide distribution and transport in terrestrial and aquatic ecosystems - A critical review of data / Plutonium, Neptunium

  P.J. COUGHTREY, D.J. JACKSON, C.H. JONES, P. KANE, M.C. THORNE
  A.A. BALKEMA Publishers, 1984, Vol. IV: 565 pages

- Radionuclide distribution and transport in terrestrial and aquatic ecosystems - A critical review of data / Americium and higher actinides

  P.J COUGHTREY, D.J. JACKSON, C.H. JONES, M.C. THORNE
  A.A. BALKEMA Publishers, 1984, Vol. V, 359 pages

- Radiation protection of the public in respect of consumer goods containing radioactive substances - A guide on the radiation protection criteria

  Group of Experts
  Report EUR 9290, 1984, 25 pages

- 4th Seminar on the radiation protection dosemeter intercomparison programme - photon dosimetry

  Proceedings of the Seminar, Bilthoven, 25-27 October 1982
  Report EUR 9192, 1984, 370 pages

- Council Directive of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment. - Council Directive of 3 September 1984 amending Directive 80/836 Euratom as regards the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation

  Report EUR 9728, 1985, 160 pages

- Progress Report of the Radiation Protection Programme 1980-1984 (Final Report)

  Report EUR 9733, 1985, Vol. I + II: 2300 pages

- Protocol for X-ray dosimetry

  J. ZOETELIEF, R.W. DAVIES, J.J. BROERSE

  Report EUR 9507, 1985, 105 pages

- Criteria and methods for quality assurance in medical X-ray diagnosis

  Proceedings of a seminar, Udine, 17-19 April 1984
  edited by G. DREXLER, H. ERISKAT, H. SCHIBILLA
  British Journal of Radiology, Supplement N° 18, 1985, 200 pages

- Behaviour of radionuclides in estuaries

  Proceedings of a seminar, Renesse, 17-21 September 1984
  Document N° XII/380/85, 1985, 442 pages

- 5th Symposium on neutron dosimetry

  Proceedings of the Symposium, Neuherberg, 17-21 September 1984
  edited by H. SCHRAUBE, G. BURGER, J. BOOZ
  Report EUR 9762, 1985, Vol. I + II: 1297 pages

- Metals in bone

  Proceedings of a symposium, Angers, 11-13 October 1984
  edited by N.D. PRIEST
  Report EUR 9250, MTP Press Ltd., 1985, 464 pages

- The behaviour of technetium in the environment

  Proceedings of a seminar, Cadarache, 23-26 October 1984
  Report EUR 10102, Elsevier Applied Science Publisher, in press, about 300 pages

- The radiobiology of radium and thorotrast

  Proceedings of a symposium, Neuherberg, 29-31 October 1984
  edited by W. GOSSNER, G.B. GERBER, U. HAGEN
  Strahlentherapie, Sonderband, in press, about 300 pages

ANNEX VI

Budgetary situation of the

Radiation Protection Programme

1981 - 1984

Total costs of the research contracts and financial participation of the Commission.

Sector *	Total Costs (ECU)	(%)	Funding CEC (ECU)	(%)
A	16.245.372	13	5.418.147	12
B	24.890.581	20	7.333.840	17
C	18.256.600	15	6.167.874	14
D	21.166.659	17	6.454.893	15
E **	25.178.551	21	12.081.147	28
F	17.228.442	14	6.192.000	14
Total	122.966.205	100	43.647.901	100

* A : Radiation dosimetry and its interpretation.

B : Behaviour and control of radionuclides in the environment.

C : Short-term somatic effects of ionizing radiation.

D : Late somatic effects of ionizing radiation.

E : Genetic effects of ionizing radiation.

F : Evaluation of radiation risks.

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