COMMISSION OF THE EUROPEAN COMMUNITIES

Directorate-General
for Research, Science and Education

Biology, Radiation Protection
and Medical Research

Directorate-General
Employment and Social Affairs

Direction
Health and Safety

RADIATION PROTECTION PROGRAMME

1976 – 1980

Synthesis of Results

MAY 1982

XII/340/82

FOREWORD

The present report contains a synthesis of the results which have been obtained in the framework of the Radiation Protection Programme of the Commission during the period 1976-1980. Its objectives are to provide, for the period considered, a short inventory of significant results and achievements which contribute to the evaluation of radiation hazards and to the protection of man against ionizing radiations, and to outline briefly some essential features (aims, budgetary means, management principles) of the programme.

The services of the Commission wish to express their deep gratitude to Professors D.W. van Bekkum, A. Cigna, Drs J.A. Dennis, L. Fitoussi, Professor W. Gössner, Dr H. Jammet, Professors A.M. Kellerer, N.O. Kjeldgaard, Sir Edward E. Pochin, Professors L.V. Pozzi, F.H. Sobels and Dr A.N.B. Stott, members of the Advisory Committee on Programme Management "Biology - Health Protection", who reviewed the synthesis prepared by the staff of the Commission for each of the sectors of the research programme.

F. VAN HOECK

A.E. BENNETT

COMMISSION OF THE EUROPEAN COMMUNITIES

SYNTHESIS OF RESULTS

obtained in the framework of the

RADIATION PROTECTION PROGRAMME

during the period 1976-1980

Content

1 : INTRODUCTION

1. PURPOSE AND OBJECTIVES OF THE RADIATION PROTECTION PROGRAMME

The Radiation Protection Programme of the Commission of the European Communities is based on the treaty which established the European Atomic Energy Community. Its purposes are to promote the study of the harmful effects of radiations on living organisms and the development of adequate prevention and protection measures and corresponding safety standards, radiation detection, radiation measurement and therapy to counteract the effects of radiation. The programme, in other words, aims at the study of the impact of radiations on man and on his environment and at the establishment and improvement of all measures necessary for prediction, prevention, protection and therapy.

Since 1959, date at which the first Radiation Protection Programme was implemented, four consecutive programmes have been executed by the Commission in the Community. The continuity of this action has been and still is necessary in view of the continuous expansion in the exploitation of nuclear energy, in the handling of waste, effluents and fuels throughout their cycle and because the evolution of nuclear plants, their decommissioning and the increase of the use or production of ionizing radiations and radioisotopes in medecine and by industry clearly calls for an evolution of prevention and control measures. As a matter of fact, carefully planned and implemented research in radiation protection at the Community level and elsewhere in the world during the last decades has assured a high standard of safety in the nuclear industry in spite of the increasing number of nuclear sites and the accumulation of irradiated fuel or high-activity material.

The contribution of the Commission programmes to the protection of man and of his environment is concretized through the preparation of basic standards for protection against ionizing radiation and through the increase and classification of scientific knowledge which not only enables the continuous adaptation to progress and experience of the safety standards but also opens new alleys to diagnosis and therapy. In this respect the Commission, by virtue of its multiple relations with all important European scientific institutions engaged on the study of radiation effects, is able to recognize and define research needs as soon as they arise and to tackle them together with those institutions in Europe which are most advanced in research on the specific problems concerned. The Commission is placed, in the course of this work, in an ideal situation for organizing research in such a manner that duplication of efforts and important research gaps are avoided within the Community; it is not, in this respect, the least merit of the Radiation Protection Programme that it has created in Europe a climate of co-operation where scientists have become members of a large European society, carefully subdivided in ad hoc working groups, where information is regularly circulated and discussed and where problems are studied in common.

The Radiation Protection Programme of the Commission also provides a consistent base of support which is vital for experiments of long duration, such as those on the late effects of radiation, epidemiology, radioecology, and for the promotion, at the molecular level, of the understanding and tools which ultimately shall enable man to follow more rational approaches in his attempts to predict the evolution of radio-induced lesions and to prevent the establishment of damages. Such efforts, if one excluded the stimulation from the Commission, would rapidly decline in Europe because the scientific skills and monetary engagements tend, nowadays, to be reduced by the governments or are diverted towards technological research and the control of molecular and cellular mechanisms for agricultural and industrial development. Finally, the Commission of the European Communities may speak clearly on

controversial issues related to radiation protection. There is thus a guarantee of objectivity throughout the various phases at which the Radiation Protection Programme is conceived and implemented and the results interpreted and communicated at large.

2. ESSENTIAL FEATURES OF THE 1976-1980 RADIATION PROTECTION PROGRAMME

2.1 Research aims

These have been, during the years 1974 and 1975, defined by numerous groups of experts which included Commission staff, participants to the previous programme (1971-1975), representatives of the main European organizations active in radiation research and high-level scientists not previously involved in the Radiation Protection Programme of the Commission. The conclusions drawn by the services of the Commission from this consultation and from the various sources of information available in the world were summarized in the document "Radiation Protection Programme 1980-1984 : research priorities and scientific documentation" (XII/1067/1979) which accompanied the proposal of the Commission at the time it was evaluated before Council decision.

The research aims of the programme, such as they appear in the decision taken by Council (O.J. of 15.3.76) and are briefly summarized in figure 1, covered the sectors of activity which had subdivided the programme in the past, as well as a new area of research and analysis specifically centred upon the evaluation of radiation risks. The creation of this sector is illustrative of the intention of the Commission to adapt, as much as possible and as much as needed, the Radiation Protection Programme to the new principles of optimization and limitation in radiation protection. These principles are based on a risk and detriment concept and require, among others, the evaluation of the socio-economic consequences of irradiation and the assessment of realistic relationships between collective dose and collective

health detriment. This shift in orientation was not carried out at the expense of the basic analysis which is still needed for the understanding and control of radio-induced damages but it is important to note, in all sectors, a very significant trend in favour of research directly executed on mammals and human cells. Experimental test systems chosen for their simplicity in spite of wide differences with human tissues were not used as widely as in the past and it is of interest in this connection to observe, for instance, that microorganisms, utilized at almost 100% in the earlier Radiation Protection Programmes for the analysis of the biochemistry and genetics of sensitivity and repair, have now been replaced in more than 60% of the cases by cultures of animal and human cells. Thus, the Radiation Protection Programme of the Commission, such as it appears in this synthesis of results for the 1976-1980 period and in the programme (1980-1984) presently under execution, is clearly oriented towards the assessment of detriment in man himself and upon the quantification of effects.

2.2 Implementation of the 1976-1980 Radiation Protection Programme

An accurate description of most of the elements which regulated the implementation of the programme can be found in the "Catalogue of Contracts" edited in 1979 by the Commission (Doc. XII/919/79). In summary, the ways followed and the means available for this implementation were the following.

Selection of research proposals and contracting laboratories :
After publication of the call for tenders a total of 209 research proposals were received. Of these, and with the help of the Advisory Committee for Management of the Radiation Protection Programme (see list of members in Table 1), 163 were selected by the Commission. As in the past programmes, cost-shared contracts, with a participation of the Commission ranging from 25 to 50%, were negotiated which clearly defined the research work to be undertaken and the rights and duties of the Commission and of the contracting laboratories. The list of contractants, classified by sector of activities, who participated to the research programme

is given in Annex 1; the geographical distribution of contracts appears in Annex 2. Among the contracts signed by the Commission, 44% originated from National Research Institutions and 39% from Universities.

Budgetary means : The budget of the 1976-1980 programme was 39 MioECU [1] which broke down into an expenditure of 76% for contractual activities including staff of the Commission working in contracts, 16% for the Biology group at Ispra and 8% for scientific management of the programme and administration. The contribution of the Commission to contractual research averaged 160.000 ECU per contract with a mean contribution to the total cost of the research approximating 34%. As can be seen from Table 2, which provides the breakdown of expenditures in the six sectors of research, the total expenditures in research contracts and for the Biology Group at Ispra amounted to more than 80 MioECU.

Commission staff assigned to the programme : During the 1976-1980 period, the contribution of the Commission to the programme was not restricted to the distribution of research funds and to the administration of the contracts. A staff of 8 scientists worked in the Biology group at Ispra for punctual execution of specific research efforts. In certain cases the Commission's staff also worked in the contracting laboratories where they were responsible for certain research projects or for certain phases of the research programme.

The Commission's staff, through its active participation, not only tried to increase the size and quality of the Community effort in radiation protection but also to stimulate the transfer of information between the Commission and the contractants. It has provided the services of the Commission with an expertise continuously exposed to the conditions which are specific of research in radiation protection.

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(1) The conversion rate of one ECU is not constant. In the middle of the 1976-1980 programme (as per 1.1.1978) 1 ECU corresponded to BFR 39.55, DKR 6.95, DM 2.51, FF 5.77, HFL 2.71, IRL 0.675, LIT 1132.46, UKL 0.675.

Table 1

Members in 1976/1980 of the Advisory Committee on Programme Management

BELGIQUE - BELGIE

M. ERRERA
A. LAFONTAINE (Chairman 1976)
P. LEJEUNE
J.R. MAISIN
O. VANDERBORGHT

BUNDESREPUBLIK DEUTSCHLAND

W. GÖSSNER
H. MUTH
W. PRINZ
R. WITTENZELLNER

DANMARK

M. FABER (Chairman 1976/1977)
N.O. KJELDGAARD

FRANCE

M. BERGES
R. COULON
L. FITOUSSI
M. GRAS
H. JAMMET
G. LACOURLY

IRELAND

J.D. CUNNINGHAM
J.W. HARMAN (Chairman 1978)
J. MASTERSON
A.W. MOORE
L.B. O'MOORE

ITALIA

M. BELLI
A. CIGNA (Chairman 1980)
P. METALLI
M. MITTEMPERGHER
G. SILINI

LUXEMBOURG

P. KAYSER

NEDERLAND

G.W. BARENDSEN
F.H. SOBELS (Chairman 1979)
L. STRACKEE
D.W. VAN BEKKUM
G. WANSINK

UNITED KINGDOM

G.W. DOLPHIN
Sir Edward E. POCHIN
A.G. SEARLE
N.G. STEWART
A.N.B. STOTT

COMMISSION

A.J. BERTINCHAMPS
P. RECHT
F. VAN HOECK

Secretariat (Commission)

H.G. EBERT
H. SCHIBILLA

Figure 1. Diagram of the main objectives of the Radiation Protection Programme and of its subdivision in the six research sectors defined on page 7

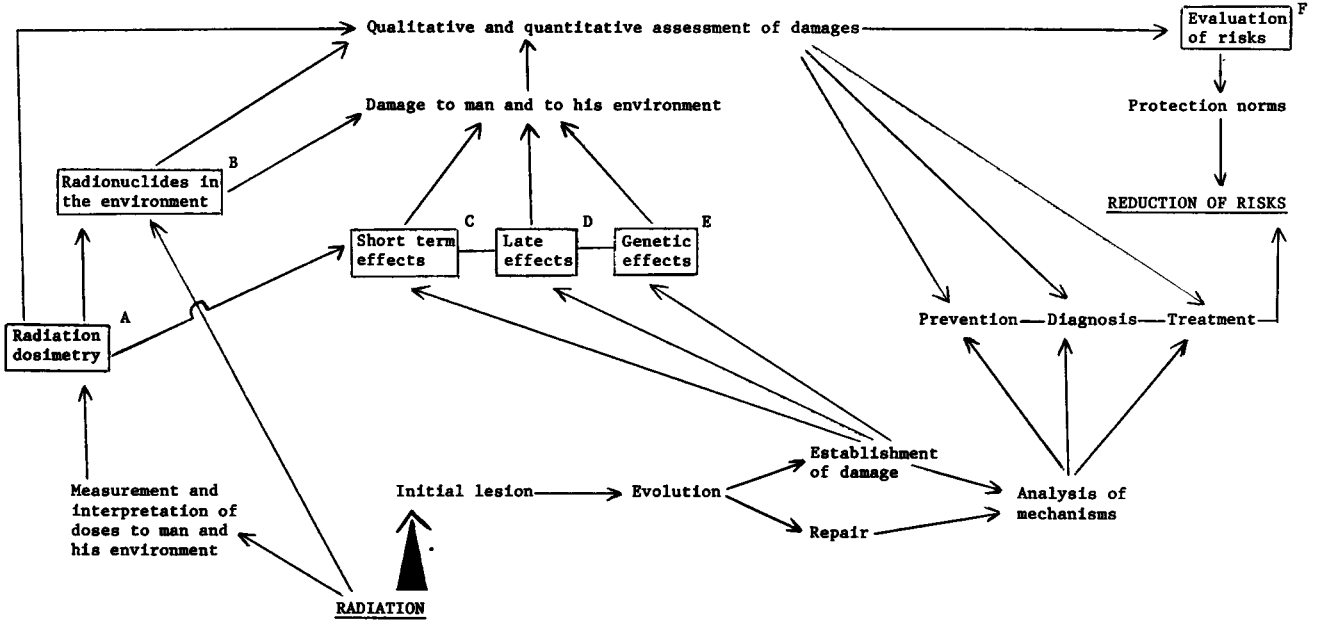

Table 2

BUDGETARY SITUATION "RADIATION PROTECTION" PROGRAMME

1976-1980

Financial participation of the Commission in research contracts

Sector	ECU	%
Radiation dosimetry and its interpretation	3.088.000	12
Behaviour and control of radio-nuclides in the environment	4.619.000	18
Short-term somatic effects of ionizing radiation	3.735.000	15
Late somatic effects of ionizing radiation	5.932.000	23
Genetic effects of ionizing radiation	5.952.000	23
Evaluation of radiation risks	2.430.000	9
Total	25.756.000	100

Total expenditures in research contracts and for the Biology Group Ispra

Sector	ECU	%
Radiation dosimetry and its interpretation	8.360.000	10.5
Behaviour and control of radio-nuclides in the environment	15.981.000	20
Short-term somatic effects of ionizing radiation	10.268.000	12.5
Late somatic effects of ionizing radiation	17.434.000	21.5
Genetic effects of ionizing radiation	23.335.000	29
Evaluation of radiation risks	5.042.000	6.5
Total	80.420.000	100

(as of 1.9.1979)

SYNTHESIS OF RESULTS

2. SYNTHESIS OF RESULTS

The synthesis of results obtained by the contractants during the 1976-1980 period is, in the following pages, presented in sectors which, in most cases, subdivide the research activities in function of the biological end-points considered by the contracting scientists. Such a classification, which corresponds to the structure adopted by the Commission for managing the programme and promoting concertation, co-operation and exchange of information between laboratories, is logical and practical. Yet, it does not prevent, particularly in those numerous cases where approaches of the contractants have been multidisciplinary, a certain discontinuity in the presentation of results. There are no fixed boundaries, for instance, between primary effects (sector C) and the cascade of events through which genetic damages (sector E) and tumoural lesions (sector D) are ultimately expressed as detriments of high socio-economic importance (sector F) in the population. Similarly, one can never dissociate completely the problems specific to the detection and measurement of doses (sector A) from the critical pathways of radionuclides in our environment (sector B) and from the identification of the sensitive targets in the living cell (sectors C and E).

On the whole, however, the classification system used up to now since the initiation of the first Community programme for radiation protection has served its purpose and has been maintained in the present review in the following order of presentation:

Sector A : Radiation dosimetry and its interpretation.
Sector B : Behaviour and control of radionuclides in the environment.
Sector C : Short-term somatic effects of ionizing radiation.
Sector D : Late somatic effects of ionizing radiation.
Sector E : Genetic effects of ionizing radiation.
Sector F : Evaluation of radiation risks.

2)

SECTOR A

MEASUREMENT AND INTERPRETATION OF RADIATION DOSIMETRY

1. PURPOSE AND GENERAL VIEW

The dosimetry sector represents a common linkage in support of the radiation protection programme as a whole. The objective of research in dosimetry is to assure that investigations on the effects of ionizing radiations be carried out properly, that the relations between radiation parameters and biological effects be understood, and that regulations for radiation protection be applied correctly and coherently within the Community. The work in this sector is therefore directed towards the determination of absorbed dose, radiation quality, and various other radiation parameters and it includes especially the interpretation of radiobiological effects and radiation risks in terms of these parameters.

The contractual work executed in 45 projects covers a comprehensive range of items in dosimetry. In more than 340 publications results were presented on such subjects as:

Realization and measurement of specific radiation protection quantities.

Attention has been paid to the relations characterizing the radiation field and to the index quantities. Considerable effort has been spent on the development of efficient approaches to the measurement and discrimination of external beta, gamma, and neutron radiation for radiation protection purposes. The description and the measurements of radiation quality, mainly for mixed radiation fields, have been duly considered.

Organ dosimetry and internal dosimetry.

Organ doses and other factors relevant to internal dosimetry were measured and calculated for both external radiations and incorporated radionuclides. For external radiations attention was given to the development of sex-specific somatic indices, in the case of X-rays, and to the problem of organ specific quality factors, in the case of neutrons. Concerning the uptake of radionuclides, several factors needed for the estimate of risk were investigated, such as dose distributions and modifying factors.

Radiation physics and microdosimetry.

The recognition that ionizing radiation transfers its energy to matter in discrete amounts has been a decisive prerequisite for the understanding of biological effectiveness and of the role of radiation quality. Thus the collection of information and data on the magnitude and on the microscopic distribution of these discrete amounts of energy (microdosimetry) is therefore fundamental to the interpretation of biological effects of ionizing radiations. It is also a prerequisite for the calculation of dosimetric parameters, such as W-values, organ doses, ranges, and stopping powers.

Interpretation of dose-effect relationships.

These studies are essential for the understanding of the correlation between biological effects, on the one hand, and absorbed dose, dose rate, and LET, on the other. These investigations, based on microdosimetric concepts, helped to elucidate mechanisms of radiation action, and in particular to extrapolate from low-dose experiments in the laboratory to low-dose exposures in actual irradiation conditions. Therefore low-dose or low-dose rate experiments provide significant guidance for the establishment of dose limits. Investigation of radiation mechanisms led to new experiments that have, in turn, provided new data on the correlation

of aberrations and tumour induction, on the radiation effectiveness for molecular lesions, and on their correlation with somatic effects.

Development of instruments and methods.

Considerable efforts have been directed towards the development of new instruments, in particular for area monitoring of neutron-gamma fields, for environmental dosimetry, personal dosimetry, and neutron spectroscopy. Apart from the special field of neutron spectroscopy where proportional counter techniques were employed, most efforts were focussed on the development of solid state dosimeters, using thermoluminescence, lyoluminescence, exo-electron emission, scintillation, and track counting in plastic foils.

Collection and evaluation of dosimetric data,
Intercomparison programmes.

This area of activity is important from the dual standpoint of radiobiology and protection. The precision and accuracy of absorbed dose measurements has been improved considerably, in particular for the dosimetry of fast neutrons. This involves not only the improvement and standardization of dosimetric instruments, methods, and calibration facilities, but also the evaluation of relevant parameters and properties for dosimetric materials, such as W values, kerma factors, stopping powers, and ranges. Of particular value in this work was the organization of intercomparisons among different laboratories in the Community and with laboratories in the USA.

Biological and accident dosimetry.

The development of a new low-dose biological dosimeter, applicable down to 1 rad, where chromosome aberration analysis is not usable, has made considerable progress, although it is still far from applicability to man.

2. REALIZATION AND MEASUREMENT OF SPECIFIC RADIATION PROTECTION QUANTITIES

The introduction of index quantities has been discussed since the publication of ICRU reports 25 and 26 in view of the practical problems posed by the realization of these quantities. Therefore, much effort has been spent on the development of effective approaches to the measurement of external beta, gamma, and neutron radiation for radiation protection purposes. The problem has also been discussed at a European Seminar on Radiation Protection Quantities for External Exposure organized by the Commission at Braunschweig, 13-15 October 1980.

Within the framework of the contractual activities, the problem of the assessment of reliable conversion factors between free-in-air measurements of kerma and absorbed dose at various depths within the 30 cm diameter tissue equivalent sphere has been carefully investigated (NRPB, Chilton). A suitably designed sphere has been constructed that can accommodate lithium fluoride thermoluminescent discs at various depths. Dose distributions within the sphere have been measured using gamma-ray and X-ray beams of various energies, corresponding to ISO reference radiation qualities. From these results deep-dose-equivalent indices per unit kerma in air have been determined. Effective dose equivalent is generally evaluated by taking the mean doses in various tissues or organs and employing recommended weighting factors. Interface effects are rarely taken into account in evaluating the mean doses in the various tissues, although they can be important when the atomic composition of adjacent tissues are considerably different, as e.g. for bone tissue and for cells near to the bone surface. Therefore, a technique for the measurement of interface effects has been developed (PTB, Braunschweig,); it is based on a precision double extrapolation chamber in which gaseous layers replace condensed volumes to expand the geometrical dimensions.

Another aspect of the dose equivalent evaluation which is of growing concern is the quality factor to be applied, especially in the case of inhomogeneous radiation fields. Therefore, the problem of the

description and determination of radiation quality of a mixed neutron and gamma-ray field has been investigated in terms of microdosimetric concepts and techniques (KFA, Jülich). The method consists of measuring the event-size distribution in the actual radiation field and then separating in this spectrum four components corresponding to the contributions from gamma-rays, fast proton recoils, slow proton recoils and heavier ion recoils. The quality factor for the radiation field is then calculated as the mean of the quality factors of the four components, as internationally recommended, weighted by the dose fractions and the dose mean LET values corresponding to the individual components. Similar methods for the determination of average quality factors of a mixed field have been developed, for instance with only three zones distinguished in the event distribution (CEA, CEN Grenoble). Furthermore algorisms have been studied to calculate effective quality factors directly from the measured lineal energy spectra directly (Univ. Homburg). This microdosimetric technique is based on the use of a single proportional counter and is likely to be extended to practical dosimetry of mixed neutron and gamma-ray fields; it offers then an alternative to more conventional methods based on the use of pairs of detectors with differential sensitivity to the two field components. This proportional counter method has most attractive features for use in radiation protection.

Some controversy has arisen concerning the additivity of index quantities with respect to energy and direction of the incoming radiation and the introduction of some modified operational quantities has been suggested for practical purposes. This would require the realization of conversion factors between beam parameters and such operational quantities, necessitating detailed knowledge of the energy distribution of the primary radiation. A ^{3}He spectrometer for fast neutrons has therefore been developed (PTB, Braunschweig). Particular design and special care spent in the construction will guarantee a high performance of this instrument, which utilises a sophisticated pulse-discrimination system.

The services of the CEC had been informed in detail by the International Commission on Radiation Unit and Measurements (ICRU) on its continuing development of recommendations on different aspects of dosimetry. In particular, the ICRU has published recommendations on quantities and units of radiation and radio-activity, on procedures suitable for the measurement and application of these quantities, and on physical data needed in the application of these procedures.

3. ORGAN DOSIMETRY AND INTERNAL DOSIMETRY

With the introduction of the new ICRP concepts, the determination of organ doses for external radiations and incorporated radionuclides has become essential to the realization of radiation protection quantities.

For beta dosimetry a still open question is the choice of the most appropriate quantity to be measured for the purpose of assuring an adequate protection to the various organs or tissues exposed. Depth-dose distributions have been measured (NRPB, Chilton), for a variety of beta-emitters, and doses at 0.3 and 0.007 cm depths have been considered in particular, since they are taken to be representative of the doses to the eye-lens and skin. The results indicate that it is possible in rather rare circumstances for the present ICRP dose-equivalent limit to the eye-lens (150 mSv) to be exceeded while the dose equivalent to the skin remains below the current ICRP limit of 500 mSv. Therefore, the depth of 0.007 cm is possibly not a suitable value for beta dosimetry in radiation protection.

For fast neutrons, radiation transport calculations were performed for approximate determinations of organ doses in anthropomorphic phantoms. Using the MIRD phantom organ doses were determined as a first step in terms of mean spectral neutron fluences (GSF, Neuherberg). They can now be converted into KERMA as well as dose equivalent by means of prepared conversion functions based upon known KERMA tables, recoil- particle distributions, and Q(L)-relations.

For X-rays, organ doses were calculated with Monte Carlo codes for the shape and size of the male reference man. Calculations were extended to include also breast, uterus and ovaries (GSF, Neuherberg). The concept of effective and somatic dose equivalent led to the decision to specify the human phantom in proper male and female versions. This resulted in two new sex-specific Monte Carlo codes, ADAM and EVA, which calculate sex-specific organ doses as well as effective and somatic dose equivalent.

For the evaluation of organ doses it is important to gain information on the influence of the geometry of irradiation on local changes of radiation quality with external radiation sources and on the resulting biological effectiveness. The variation with the position in a human phantom of the effectiveness of radiation for cell reproductive death has therefore been investigated (TNO, Rijswijk), a collaboration between European laboratories. High-energy alpha particles and fast neutrons were used for this. Parallel measurements of microdosimetric parameters were carried out for different irradiation conditions and for different geometrical positions in the phantom. The results appear to indicate that in actual irradiation situations the biological effectiveness may vary as less than it could be expected from the measured changes in the microdosimetric distributions of lineal energy. Similar conclusion can be drawn from the results of radiobiological experiments in mixed neutron and gamma-ray fields on the induction of chromosome aberrations in human lymphocytes and on the impairment of proliferation of mammalian cells (Univ.Homburg). Here too, measurements performed at various positions in a water phantom have indicated that the biological effectiveness of neutrons does not vary substantially with the position in the phantom, even not outside the primary beam. Another investigation of the biological effectiveness of mixed neutron-gamma fields, using cultured mammalian cells irradiated at different positions in a water phantom, and of the corresponding microdosimetric spectra, came to the same conclusion (KFA, Jülich). It was also possible to establish a theoretical relationship between y^*, the dose mean lineal energy corrected for saturation, and RBE.

The problem of radiation risks related to incorporated isotopes is presently gaining considerable attention in the framework of radiation protection, as indicated by the interest recently demostrated by international organizations on this matter.

Radiobiological effectiveness of incorporated radionuclides emitting low-energy electrons, namely ^{3}H, ^{123}I, ^{125}I, ^{64}Cu and ^{75}Fe, was investigated in comparison to external radiations (KFA, Jülich). Particular attention was given to the question of the magnitude of the transmutation effects of these radionuclides when incorporated into the DNA, in comparison to the radiation effects of the low-energy electrons emitted. For this scope, calculations relative to the mode of disintegration and the energy deposition processes were performed, leading to the development of a model for the biological effect of radionuclides incorporated into DNA. In this model transmutation effects are related to the number of positive charges left on the DNA, whereas the radiation effects are related to the energy locally impart to DNA by the electrons emitted. The importance of this problem for radiation protection lies in the fact that mutations are especially significant for long term effects and that mutations and single strand breaks may be drastically increased by disintegrations in the DNA, as in the case of DNA-bound tritium. Therefore, single and double stand breaks produced by incorporation of ^{3}H and ^{125}I in isolated DNA and in intact mammalian cells in culture were measured, together with cell survival. The results are quite interesting: they show that for tritium disintegrating in DNA transmutation effects are particularly relevant for the production of single-strand breaks.

Finally, the question was investigated of how and to what extent the existence of inhomogeneous microdistributions of tritium may affect radiation protection recommendations. This was done in a study on the incorporation, metabolism, and excretion of tritiated DNA and RNA precursors in mice. By defining 4 different modifying factors that characterize metabolism, local dose distribution, effectiveness

distribution and cell renewal, it was found that for tritium-thymidine the total modifying factor was 10 for ingestion and 50 for injection.

4. RADIATION PHYSICS AND MICRODOSIMETRY

The interpretation of biological effects and their implications for radiation biology depend on the completeness and precision of dosimetric data describing exposure, absorbed dose and radiation quality of the radiation used.

It is of fundamental importance that methods have been developed and improved in recent years to analyze tracks of charged particles and their secondaries, using both experimental methods and computer simulation.

A cloud chamber was employed for the measurement of ionization-track structures of alpha particles and low-energy electrons in the gas phase (AERE, Harwell), and the results were used for the determination of proximity functions, in good agreement with theoretical calculations. In the condensed phase, the presence of short tracks due to recoil nuclei was investigated, and a calculation of these heavy secondaries led to satisfactory interpretation. These results suggest that a certain contribution to radiobiological effects may be due to this mode of energy loss through the formation of arborescences of heavy secondaries (Univ. Strasbourg).

During the last four years Monte-Carlo calculations of electron tracks have been completed (GSF, Neuherberg; Univ. Toulouse). They consider individually the different electron interactions resulting in ionizations and excitations and thus they represent a new step forward in the dosimetric interpretation of biological data. These theoretical methods were used for the calculation of track structures of electrons and energetic ions and played an important role, both, for the interpretation of in-phantom measurements and for the determination of organ doses.

Theoretical work has also been performed on the transport of electrons and heavier ions in water and other media (Univ. Toulouse). In particular, the simulation of tracks of low-energy electrons in water vapour has been obtained by a Monte-Carlo code. This work is particularly interesting because it has allowed to calculate the distributions of inter-ionisation distances in the biological volume surrounding DNA, and also to evaluate proximity functions for electrons between 100 eV and 10 keV. These functions have been introduced recently in microdosimetry for the interpretation of radiobiological experiments with short-range electrons. Track structures of low-energy electrons in water vapor have also been applied to situations of multiple electron emission, such as the disintegration of 125-iodine (KFA, Jülich), and the interaction of low-energy X-rays with water molecules (AERE, Harwell). These experimental and theoretical data on particle tracks were then applied to the evaluation of different microdosimetric functions and quantities (Univ.Toulouse; GSF, Neuherberg; Univ. Würzburg; AERE, Harwell).

Calculations have also been performed for fast neutrons (Univ. Würzburg), and it has been found that, in this case, the application of proximity functions is limited by saturation effects. The concept of proximity function is also applicable to geometrical configurations and this has been utilized to demonstrate that, entirely independent of radiation quality, spherical and cylindrical proportional counters are very nearly equivalent for the measurement of average values of microdosimetric spectra.

An essential point in this and in related calculations is the knowledge of reliable total cross-sections as well as of energy and angular distributions of secondary charged-particles. The reliability of cross-section data is questionable for neutron-induced reactions at energies where non-elastic processes are dominant. Therefore the work on cross-section calculations (NRPB, Chilton) is of considerable interest. In particular, the application of nuclear models has led to nuclear cross-sections for the main elements in tissue, i.e. H, C, N, and O, and also for other elements of biomedical and dosimetric importance, such as

Mg, Al, P, S, Ar, and Ca. The conversion of particle and recoil-nucleus energy spectra for the above elements into kerma values will be one result of this work.

In order to obtain better information on the double differential distribution of secondary electron emission, the transport properties of low-Z materials for electrons in the track of 1 MeV protons, as well as for source electrons have been investigated by means of a specially constructed spectrometer (GSF, Neuherberg). The results provide information about the electron-energy transport mechanisms in the tracks of heavier ions. In particular, high-energy electrons appear to be preferentially directed away from the ion track, whereas low-energy electrons have a nearly isotropic distribution. Consequently, the electron energy spectra become harder with increasing radial distance.

Good knowledge of the energy lost by charged particles per unit distance in a given medium (stopping power) and of the mean energy expended in a gas per ion pair formed (W-value) is of fundamental importance for the understanding of the processes of energy transfer by radiation to matter and for the computation of most dosimetric quantities, especially when using ionisation chamber techniques. W-values of electrons from 5 to about 500 eV in various gases and gas mixtures were measured as needed for the use of gas chamber dosimetry (GSF, Neuherberg). As the quoted experimental errors are less than 2 %, these results seem adequate to resolve previous discrepancies between data from various authors, as to the energy dependence of electron W-values. W-values of electrons up to 2 keV were measured in another investigation (KFA, Jülich). In the overlapping region, between about 100 and 500 eV, the two series of data agree fairly well.

Also W-values for ions have been measured in gases and gas mixtures most frequently encountered in ion chamber dosimetry. In particular, the energy dependence of W has been determined for H, He, C, O, and Ar ions with energies between 10 keV and 400 keV in argon, nitrogen, methane,

carbone dioxide and in different gas mixtures (CEA, CEN Fontenay-aux-Roses). Similar work for ions with energies in the region between 5 and 100 keV has been undertaken, together with a thorough revision of the existing models for W-calculations (Univ. Dundee). Although comparison of experimental data with calculated values often yields satifactory agreement, especially in the case of heavier ions, existing discrepancies cannot yet be fully resolved, and the attempt of a thorough evaluation appears to be necessary. A similar conclusion can be drawn from the results of work carried out on a more limited scale (NRPB, Chilton) to measure W-values of the ions in the range of 1 MeV to 4 MeV for gases of dosimetric importance, namely Rossi's tissue-equivalent gas and its constituents.

Analysis of values in the literature has indicated that stopping powers for charged particles in condensed media of low mean atomic number may be significantly lower than in the equivalent gaseous or vapour phase. From these data it was estimated that for neutrons, too, the effective stopping power in the gaseous phase may exceed that in the condensed phase by up to 8 % at 0.1 MeV and up to 3.2 % above 5 MeV. Therefore various experimental methods have been elaborated for the determination of stopping power values in solids, liquids and gases (Univ. Dundee). Measurements of stopping powers have been carried out for alpha particles with energies between 0.5 and 5.5 MeV indicating a phase effect of up to about 4 %. Measurements have also been planned and are in progress on a number of hydrocarbons in solid, liquid and gaseous forms. In particular, measurements of stopping powers of alpha particles have been carried out in polyethylene films and ethylene gas (NRPB, Harwell). The results confirm that a certain phase effect is present. However, in no case do the differences between gaseous and solid phases seem to exceed 5 %. As to the absolute values of stopping powers of various particle types, it seems that existing discrepancies between data sets cannot yet be solved, especially at low ion energies. In particular, a study of charged-particle ranges (CEA, CEN Fontenay-aux-Roses) has shown that for ions heavier than helium the extrapolated ranges may differ appreciably from the values used acutally. Therefore an experimental study of stopping powers and ranges of intermediate and low energy ions in organic

media has been undertaken using nuclear track emulsions submitted to a latent image-activation development process (Univ. Strasbourg). In parallel, a theoretical evaluation of the contribution of electronic and nuclear stopping powers for heavy charged particles of low and intermediate energy in biological tissue has been initiated. A study of the influence of the physical state of some non-polar compounds on the ionisation potential for low-energy photon interactions has also been performed (Univ. Toulouse), and it has been demonstrated that the ionization potentials are significantly different for materials in their gaseous and their condensed state.

The distributions d(y) and the frequency and dose mean $\bar{y}_F$ and $\bar{y}_D$, now often employed to describe radiation quality, have also been determined experimentally for a large variety of radiations. With proportional counters such data were measured for X- and gamma-rays, for fast neutrons of up to 19 MeV, and for broad neutron spectra from different neutron-therapy units (Univ. Homburg; KFA, Jülich; CEA, CEN Grenoble) as well as for pi-meson beams (Univ. Homburg). Calculations of d(y) and $\bar{y}_D$ of fast neutrons were also performed and the results compared to experimental data (GSF, Neuherberg). Most of the experimental and calculated data were obtained not only for free-in-air exposure but also at different locations in a water phantom.

5. INTERPRETATION OF DOSE-EFFECT RELATIONSHIPS

This problem, fundamental to the assessment of risks for radiological protection, has found continuous attention since the discovery of X-rays. The progress report 1976-1980 lists a substantial number of projects tackling this problem both experimentally and theoretically. A general theory of radiation mechanisms valid for all types of radiation is still missing, nevertheless considerable progress has been made with regard to the low-dose-problem. It was due to microdosimetric principles that single-event and multiple-event probabilities could be calculated and that the correlation was established between single-event effects and linear kinetics on the one hand and multiple-event effects and non-linear

kinetics on the other. This led to the realization that, given sufficient time for repair, there is no difference between the effectiveness of radiation at low-doses and at high doses delivered with low-dose rate. Accordingly, experimental data obtained with normal doses and sufficiently low dose rates might be extrapolated down to the low dose levels of interest in radiation protection. This is the theoretical background of a number of investigations on low-dose effects.

The variability of RBE values for cell reproductive death and chromosome aberrations among different types of cultured mammalian cells has been investigated (TNO, Rijswijk), together with the dependence of RBE on neutron energy. The results indicate a marked variability in the sensitivity of the various cell lines for the end-points considered. As expected, RBE values for 0.5 MeV neutrons were found to be higher than those for higher neutron energies, a maximum of about 12 was observed for V-79 cells at 50 percent survival.

Investigations of RBE of fast neutrons have been carried out at low neutron dose levels in an attempt to reassess the quality factors for neutrons (CNEN, CSN Casaccia). Measurements of biological responses to fast neutron and photon beam irradiations were performed on a variety of biological systems in-vitro as well as in-vivo. In particular, data on eye-lens opacification in mice were determined for a wide range of neutron energies. The results of these measurements, especially the progression of the number of radiation induced opacities with post-irradiation time, provide a very useful contribution to the understanding of the mechanisms of opacity induction by radiation. They have also stimulated further research on the type of radiation damage produced. Therefore additional neutron irradiations of the murine eye lens have been carried out to investigate the energy and dose dependence of the production of micronuclei. In parallel, a large carcinogenesis experiment on the induction of ovarian tumors in mice has been undertaken. In general, the results obtained indicate that neutrons may become increasingly effective per unit dose at decreasing doses. Irradiation of cultured plant cells with fast neutrons have also shown that a fractionation in small doses below a certain low level, can cause

a substantial increase of neutron-radiation effectiveness. If confirmed, these results may be of considerable significance for radiation protection. Typically, neutron RBE values around 30, relative to absorbed neutron doses of the order of 10 mGy, have mostly been observed in the above experiments. The problem of saturation by an excess of energy deposition by single events in the sensitive cellular region has also been investigated and a quantitative formulation of the effect of saturation has been proposed for cell survival curves after exposure to high-LET radiation.

In the determination of radiobiological data at very low dose levels one faces difficult statistical problems. A very substantial effort has therefore been directed towards the refinement and further development of sophisticated mathematical methods of data analysis. These methods have then been applied to the results of extensive animal experiments aimed at elucidation of the radiation carcinogenesis at low doses of sparsely and densely ionizing radiations (Univ. Würzburg). Using these powerful mathematical methods of data analysis, it could be shown that the very small single dose of 1 mGy of neutrons accelerates the spontaneous incidence of mammary neoplasms in Sprague-Dawley rats by more than 30 days, corresponding to an RBE larger than 100. Furthermore sublinearity at low neutron doses was found, i.e. the effect produced per unit dose at 1 mGy neutron dose was higher than the effect produced per unit dose at 4 mGy. Only a very small fraction of cells receive any energy deposition at the dose levels considered, and this was shown to imply that the induction of the neoplasms cannot be merely proportional to the rate of cellular transformation, but that tissue effects must govern the dose dependence. Neutron RBE values are derived at low dose levels that largely exceed the quality factor of 10, that is presently used for neutrons in radiation protection.

Since Spargue-Dawley rats are known to have an atypically high spontaneous incidence of mammary neoplasms, an analogous experiment was conducted with ACI rats, a strain with almost no spontaneous incidence of mammary neoplasms, but with a substantial induction of mammary adenocarcinomas by the synthetic hormone DES (Univ. Würzburg). The

essential findings of this experiment are that a substantial sublinearity in the dose-effect relationship for neutrons has again been established in the case of DES treated animals, whereas a linear dependence is observed for X-rays. RBE values in excess of 100 were reached at a dose of 10 mGy of fast neutrons. These results indicate, therefore, the possibility of synergistic effects also for densely ionising radiations, and they substantiate the high RBE-values predicted on the basis of microdosimetry. Furthermore, they throw doubt on the general validity of linear extrapolation at low doses.

Data of experiments on the induction of malignant pulmonary neoplasms in rats due to radon inhalation have been analysed and they suggest a dose dependent acceleration factor for the tumor prevalence; they also seem to exclude the possibility of a threshold at low doses.

Concerning the analysis of leukemia and other neoplasms in the survivors of the atomic bomb explosions, an extensive methodological investigation has been continued, but the actual numerical evaluations have to await the final outcome of the present dosimetric reassessment.

Understanding of the mechanisms of biological action of radiation is related to the clarification of the physicochemical and chemical processes underlying the production and repair of biological damage. A detailed investigation of these processes has been carried out (Univ. Homburg); it includes measurements of free electrons and H-radicals in water samples in the absence, as well as in the presence, of radical scavengers and measurements of chromosome aberration rates produced by X-rays and low-energy beta rays at various temperatures. In addition, measurements of radicals produced in water with the addition of solved cell nucleus compounds have been initiated both with low- and high-LET radiations. From the results of the various measurements in-vitro, interaction parameters such as the site diameter or the probability of aberration induction have been determined. Much work appears to be still necessary on these subjects, however, some essential conclusions can already be derived, e.g. that damage in the repair system may occur simultaneously with the first chromosome break in the cell. The problem

of DNA double-strand break repair was extensively studied on yeast cells irradiated with 30 MeV electrons or with 3.5 MeV alpha-particles (GSF, Frankfurt). These cells are the only eukaryotes in which induction and repair of double-strand breaks can be studied at the same radiation doses which are used in survival studies. The results obtained so far suggest that they are potentially lethal lesions. The shoulder of dose-response curves with immediate plating is due to repair of potentially lethal lesions within a short time period. In addition, double-strand breaks appear to be induced exclusively by direct radiation action, whereas indirect action is negligible. A comparison of the data for electrons and alpha particles suggests that the types of repairable double-strand breaks are the same for both sparsely and densely ionizing radiations, and the difference in effectiveness may result only from a difference in the relative numbers of repairable and irrepairable double-strand breaks.

Concepts of models of radiation action (Univ. Dundee) have been studied critcially. In particular, cross sections for inactivation of ribonuclease by low-energy heavy ions have been measured with the aim to see whether the enzyme-inactivation cross section as a function of incident particle energy would be more closely related LET or event frequency. From the results the authors have deduced that the event frequency plays the dominant role in radiation action, rather than the energy deposition. In parallel, calculations of inactivation cross-sections have also been performed and a new model of radiation action has been proposed which is based on the one-hit one-target concept and gives separate consideration to direct and indirect radiation effects.

6. DEVELOPMENT OF RADIATION PROTECTION INSTRUMENTS

In radiobiological studies it was repeatedly shown that neutrons have the largest RBE in the energy region between 0.1 and 1 MeV, in good correspondence with the fact that the dose mean lineal energy has a relative maximum in this energy region for soft tissue and that saturation of biological effect is apparently still negligible at these neutron energies.

Therefore, in respect to radiological protection, particular attention is given to neutrons below 1 MeV. This implies that neutron dosimetry cannot just be limited to the MeV region by the cut-off in sensitivity of currently used detectors, but must extend to lower neutron energies. For this reason, conventional dosimetric techniques, based mainly on the detection of ion recoils produced by the primary radiation, and which are well suited for neutron dosimetry in the MeV region, have to be complemented by other techniques characterized by high sensitivity to lower energy neutrons. In particular, techniques based on the albedo effect have recently been given considerable attention. It has been shown, in fact, that a suitable combination of albedo and ion-recoil based detectors may have a neutron-energy response which simulates fairly well the energy dependence of the quantity dose equivalent in soft tissue for a broad region of neutron energies. For this reason, an extensive investigation of plastic dosimeters for the detection of albedo neutrons and neutron produced recoils has been carried out (CNEN, CSN Bologna). In particular, it has been shown that the use of suitably manufactured CR-39 plastic detectors, together with a chemical etching process, allows to reduce the problem of background tracks, usually encountered in polycarbonates, down to a level acceptable for the use of these detectors in radiation protection. Furthermore a dosimeter using a combination of albedo and thermally-stimulated-electron-emission (TSEE) type detectors has been constructed (CEA, CEN Fontenay-aux-Roses). Mechanical stability, together with ease of handling, has been especially sought for. In general, the results obtained by these dosimetry methods, although not conclusive, are fairly encouraging.

Multi-element detectors have also been studied (CEGB, Berkeley), which would be used for the determination of microscopic distributions of dose in a solid medium. In particular, a neutron detection system has been developed which has rem-response over the energy range from thermal to about 10 MeV.

A complete neutron monitoring system for use in nuclear fuel processing plants has been designed and constructed (AERE, Harwell). It consists of several parts, namely integral dosimeters, pocket alarm devices, survey instrumentation, dose equivalent rate monitors and neutron spectrometers. Expected large variations of dosimeter response due to largely variable neutron spectra in processing plants suggested that the use of albedo technique for the measurements of dose equivalent should be avoided and that (n,fission)-type detectors are to be preferred.

The physical processes underlying the performances of materials used in solid-state dosimetry, mainly thermoluminescence and lyoluminescence, have been investigated. In particular, the effects of LET on the thermoluminescence response and light-conversion efficiency of lithium fluoride and borate have been studied for a number of radiation qualities at absorbed doses up to 10^5 Gy (NRPB, Chilton). It has been proved that lithiumfluoride dosimeters are potentially useful for mixed-field dosimetry when the LET components of the field are known.

The applicability of the phenomenon of lyoluminescence to the dosimetry of radiations with different LET has also been investigated with the aim of developing a simple and sensitive personal and accident dosimeter (Univ. Aberdeen). An efficient and reliable reader for lyoluminescence has been designed and the response of different phosphors to radiations of various LETs has been studied, including incorporated radionuclides as well as fast and thermal neutrons.

An important problem in the use of low-energy neutron detectors is represented by their calibration, especially in the epithermal region. Therefore a certain interest is attached to the design of an

intermediate-energy neutron facility (CEGB, Berkeley), which is based on the use of transmission filters placed in the beam channel of a research reactor, and would be capable to give several quasi monoenergetic neutron beams between 60 eV and 120 keV.

Improvement of the dosimetry of beta radiation for radiation protection monitoring was investigated in a study on beta dosimetry with semi-conductor detectors (KFA, Jülich). It was shown that it is possible with the help of surface-barrier detectors to determine the dose rate from small values up to 14 Gy/h with fairly constant sensitivity. It was also shown that the sensitivity of the detectors to 137-Cs gamma radiation was equal to that for beta radiation.

7. COLLECTION AND EVALUATION OF DOSIMETRIC DATA AND METHODS, INTERCOMPARISON PROGRAMES

The need for dosimetry intercomparison programmes has become more and more evident during the past years. In experimental radiobiology the difficulties of measuring doses reliably are well known, and discrepancies in dosimetry performances have repeatedly been made evident by past intercomparisons such as INDI and ENDIP. In pratical protection it has been suggested that intercomparisons of personal dosimeters and monitoring instrumentation need not only be performed in standard radiation fields, but also under realistic occupational conditions.

Suitable neutron calibration facilities have been completed (GSF, Neuherberg) and already used for the European Neutron Monitoring Intercomparison Project (ENMIP). In addition, laboratories have participated in several other intercomparisons of monitoring instrumentation, accidental dosimetry, etc. For the institutes cooperating within the European Late Effects Project Programmes (EULEP), intercomparisons of doses and dose distributions have been performed (ITAL, Wageningen). These intercomparisons, carried out with mailed thermoluminescent dosimeters, resulted in improvements of the accuracy and precision of the X-ray dosimetry at the EULEP laboratories.

In 1976 a committee was set up to collect and evaluate neutron dosimetry data (CENDOS). The activity of this committee was initially determined by the problems that emerged from an intercomparison project in neutron dosimetry (ENDIP). Later, a limited scale intercomparison has been organized to search for systematic uncertainties in the results of some of the participants. Furthermore, various commercially available ion chambers have been tested and their performances discussed during a workshop on "Ion Chambers for Neutron Dosimetry". Current knowledge on dosimetric data for neutron dosimetry has been examined and considerably improved.

The collection and evaluation of dosimetric data, not only for neutron dosimetry but for dosimetry in general, is important from the dual standpoint of radiobiology and radiation protection. The precision and accuracy depends on the knowledge of relevant dosimetric parameters, such as W-values, KERMA factors, absorption coefficents, cross sections, stopping powers and ranges. Considerable improvement has been attained in the knowledge of these data.

Assessment of effective dose equivalent is substantially based on the results of measurements of dose distributions in anthropomorphic phantoms. If gaseous TE ionisation chambers are used, the effective point of measurement can be displaced from the geometrical centre of the chamber due to the replacement of phantom material by the cavity filling gas. Corrections might need, therefore, to be applied to the actually measured dose values for changes in attenuation and scattering of the radiation. A detailed investigation of this effect has been carried out (TNO, Rijswijk) using various ion chambers with different internal diameters to measure dose distributions in the phantom for a variety of radiation qualities. The values obtained indicate that no displacement was observed for X-rays and low energy fast neutrons, whereas corrections appear to become necessary to the dose values measured in the phantom in the cases of high-energy neutrons and high-energy photon irradiation.

A comparison of neutron doses at the radiobiology and therapy levels, that are measured with ion chambers, with those derived from measurements of neutron fluence either by a proton recoil telescope or by the associated alpha-particle technique, has been completed (NPL, Teddington). Good agreement has been obtained between results of these three techniques. Under free-in-air conditions higher accuracy is obtainable from the fluence determination methods than from the use of an ion chamber. Nevertheless, for practical reasons, the ion chamber remains the preferred instrument.

An intercomparison study of whole-body monitors installed in 12 European institutes has been performed (TNO, Arnhem) as a pilot study in order to improve accuracy and uniformity in internal contamination measurements.

8. BIOLOGICAL AND ACCIDENT DOSIMETRY

Incorporation of Iododeoxyuridine (IUdR) in irradiated cells may have an interesting practical utilization for biological and accident dosimetry. Tests performed on mice irradiated at dose levels of 0.5 to 100 rad have shown that IUdR incorporation is reduced in irradiated cells. The highest sensitivity for this effect was obtained in cells irradiated in-vivo and measured in-vitro. The results also show that the magnitude of the effect depends on radiation dose, radiation quality, and time interval between irradiation and injection of the radioactive precursor (KFA, Jülich). The development of a sensitive biological dosimeter was obtained when it was discovered that the incorporation of IUdR into unirradiated cells in culture was also inhibited, if the blood serum of irradiated mice was added to the culture medium. This blood serum test is simple, fast, and applicable to man and is thus potentially a low-dose, short term, biological accident dosimeter. Partial body irradiation showed that the effect is proportional to the weight percentage of the irradiated body and does not demonstrate any specific organ reaction.

S E C T O R B

RADIOACTIVE CONTAMINATION OF THE ENVIRONMENT

1. PURPOSE AND GENERAL VIEW

In the framework of a Radiation Protection Programme, the main aim of the study on the behaviour and transfer of radionuclides in the environment is to provide the information required for the evaluation of potential doses to the population liable to result from both the operation of nuclear plants and the disposal of radioactive wastes. This information is fundamental for implementing the recent recommendations of the ICRP through the mathematical models already developed for the evaluation of individual doses and collective dose commitments. Furthermore, a better knowledge of the processes responsible for space- and time-dependent distribution of radionuclides between the various compartments of terrestrial and aquatic ecosystems, accompanied by "in situ" radioecological investigations, could provide an extremely valuable guideline to the improvement of provisional mathematical models. In particular, for long-lived radionuclides (transuranics, ^{99}Tc, ^{129}I) it is urgent to acquire more data on their migration into the environment and their transfer through the food chains. Since the behaviour of most of the radionuclides is strongly dependent upon their physico-chemical form, both thermodynamic and kinetic aspects responsible for abiotic and biotic transformations (acid-base and redox reactions, complexation, adsorption, metabolism, etc.) should be taken into consideration.

The information acquired in such studies will provide data which are the prerequisite for evaluating individual intakes of radionuclides as a function of their release into the environment.

2. SEA AND CONTINENTAL WATER ENVIRONMENTS

Evaluation of the impact of nuclear plants discharges to the marine environment was established during the programme 76-80, with special attention to the Irish Sea Water (MAFF, Lowestoft, UK), the french coastal area (Univ. Nantes/CEA, La Hague, F) ; the italian coast (CNEN, Fiascherino, I), the Thule region in Greenland (Risø National Laboratory, Roskilde, DK), the Rhine-Meuse-Scheldt estuaries (Delta Inst., Yerseke, NL) and the Meuse river (IHE, Bruxelles/Univ. Namur, B).

2.1. Distribution of radionuclides in sea water

The environmental behaviour of long-lived nuclides discharged into the marine environment has been particularly studied in past years.

Concentrations of Pu, Am and Cm in both filtrate and particulate water samples in the Irish Sea (MAFF, Lowestoft, UK) were evaluated in relation to the concentration of ^{137}Cs in the samples, the chemical speciation of Pu, and the rates of discharges of each nuclide. The three most important transuranium elements : Am - Cm - Pu are, to a varying extent, largely adsorbed onto particulate material, the adsorption of Pu depending on its oxidation state.

The distribution of ^{137}Cs and ^{134}Cs between seawater and biota in British Isles coastal waters and adjacent seas is closely related to the rates of discharges from the B.N.F.L. fuel reprocessing plant, Windscale. Moreover, it has been observed that almost all the ^{137}Cs discharged leaves the Irish Sea by the way of the North Channel, progresses northward around the coast of Scotland to enter the North Sea and finally the Baltic Sea.

The distribution of the monitored fission products in the Irish Sea has also been influenced in recent years by climatic variation : a sharp change in the flow of water has reduced the residence time and the steady state concentration of these radionuclides.

Higher discharges from Windscale in 1978 have permitted the reassessment of the behaviour of Tc-99 in the marine environment. The last observations have confirmed that it behaves conservatively in marine environment. This is in good agreement with laboratory studies which

emphasized the high stability of the anion pertechnetate (TcO_4^-, the chemical form of Tc released in sea water) in a wide range of physico-chemical conditions and the negligible importance of ion-exchange and adsorption phenomena (CNEN, Fiascherino, I).

French activities (Univ. Nantes, F) have been devoted to the distribution of principal gamma emitters released by the La Hague plant in waters of the Channel. It has been shown that the ^{144}Ce is a good tracer of the suspended particles movements (less than 0,5 % is on a soluble form in sea water) ; on the other hand ^{125}Sb is an excellent tracer of water movement and the presence of ^{106}Ru soluble forms depends upon the physico-chemical characteristics of the wastes. Ratios ^{106}Ru / ^{125}Sb in sea water were determined in an area influenced by the La Hague reprocessing plant. In the Baie de la Seine, an important quantity of ^{106}Ru is trapped by the enormous stock of suspended material which is present in this area. These conditions are responsible for a decrease of the ratio $^{106}Ru/^{125}Sb$, from 20 in Cap La Hague effluents to 6 in the Baie de la Seine waters. Dilution factors in the investigated area (relative to La Hague effluents) have been established for the different radionuclides. In the Baie de la Seine this factor is 7,5 for ^{106}Ru and only 2 for ^{125}Sb (local reconcentration phenomena). These values are far from provisional dilutions (> 100) established by models which do not consider either time-trend nor physico-chemical forms of the rejected elements.

2.2. Accumulation in the sediments

2.2.1. Sea environment

Evaluation of the impact of nuclear plants discharges in the marine environment were studied along the Italian coasts with particular reference to radioactivity release in coastal waters (CNEN, Fiascherino, I). A geomorphological classification has been used to select the most representative sampling points in the zones investigated. Mineral composition of samples together with the knowledge of the distribution pattern were considered as a basic information to study the behaviour of radionuclides in the different types of coastal sedimentary environment.

Higher ^{137}Cs concentrations in sediments were found in areas with high sedimentation rate and characterized by a large amount of small size particles. The vertical profiles of ^{137}Cs show a maximum at 8-10 cm depth ; the distribution pattern of $^{239-240}Pu$ is similar but the maximum occurs at 15-20 cm depth.

The effects of wind on deep waters of the Ligurian Sea (CNEN, Fiascherino, I) and the interaction of deep waters with coastal currents have also been studied.

The time-trend of environmental plutonium and americium levels were studied in the Thule contaminated site (Risø Nat. Lab. Roskilde, DK). The horizontal as well as vertical distributions of the activities in the sediments may be described by exponential expressions. The median distance from the point of impact increased from 5 km in 1974 to 6,5 km in 1979 and the median depth of the activity increased from 4,8 cm in 1974 to 8,4 cm in 1979 corresponding to a vertical movement of 7,4 mm y^{-1}. It has been observed that the vertical distribution was strongly influenced by bioturbation. The estimate of $^{239-240}Pu$ inventory was not different from that of previous years and there is no indication of any transfer from sediments to water of soluble Pu.

The mean level of $^{239-240}Pu$ in surface water samples is comparable to the fallout level. The analysis of filtered samples indicated that approximately 10% of the plutonium activity from fallout in seawater was particulate. The mean ratio : $^{241}Am/^{239-240}Pu$ in sea water was 0,15 and in particulates approximately 0,30. In the samples containing accident Pu (deep water) the total water showed a ratio $^{241}Am/^{239-240}Pu$ of 0,06 and in particulates of 0,12 which is similar to the ratio found in sediments. It can be concluded that Am is depleted in the water as compared to Pu ; hence the ratio of Am to Pu becomes lower in the water than in fallout and in particulates.

The more fundamental chemical parameters needed to understand the distribution and behaviour of plutonium in the aquatic environment (chemical speciation) are : 1) the oxidation state(s) of the plutonium present in seawater and 2) the extent to which each oxidation state is associated with suspended particulate matter. These two points were considered in an important study conducted by the MAFF (Lowestoft, UK) laboratories. The large difference in the distribution coefficients

(Kd) between seawater and suspended particulates of both oxidation state groups of Pu (Pu(III+IV) ; Pu(V+VI)) implies that the distribution between these phases may be highly dependent upon the ratio of oxidation states in the source material. It has been observed at Windscale that approximately 95 % of the Pu discharged is rapidly removed to the seabed and that the remaining 5 % is removed from the area by water transport in a manner indistinguishable from the transport of the soluble isotope ^{137}Cs. The concentrations of $^{239-240}Pu$ of each of the two oxidation state groups have been measured in samples of interstitial water and sediments. The concentration in the interstitial water was generally lower than the concentration measured in samples of the overlying sea water. Moreover, the dissolved Pu in the interstitial water was primarily in a reduced form while the dissolved Pu collected from the overlying water was primarily in an oxidized form. The Pu adsorbed to the solid phase was almost entirely in the reduced form. Based on the study of the concentration ratio between the solid and liquid phases it was suggested that the reduced form of Pu does not become appreciably more soluble after burial and that the rate at which plutonium could be moved through the interstitial water by either chemical diffusion or advection must be exceedingly slow.

Accumulation and release of radionuclides at the water-sediment interface depends also upon a number of factors related to both biotic and abiotic processes. The relative importance of various components of marine sediments was evaluated through the determination of trace elements in solid sediment and interstitial water, total organic carbon and nitrogen, maximal biological activity and concentration of sulphate-reducing bacteria (CNEN, Fiascherino, I).

2.2.2. Estuarine environment

The Rhine-Meuse-Scheld estuaries might be envisaged as a sink for many substances which are transported by rivers to the sea. Concentrations of $^{238-239-240}Pu$ were determined in sediment, particulate matter, salt marsh plants and lichen from various locations of the Delta area (Delta Inst., Yerseke, NL). The activities of ^{137}Cs and $^{239-240}Pu$ of deposited and suspended sediments from the delta were compared to those of other estuarine environments : the Gironde estuary which can be assumed as a

reference and the Seine Bay estuary. For both isotopes, the estuary samples show in general similar activities when compared with those measured in the Gironde estuary. In French estuaries there is systematic increase of particulate Pu along with salinity.

In the ITAL project (Wageningen, NL) attention was mainly focused on the determination of Pu in sediment samples of the Rhine river delta. First samples were taken from a clay-type soil from the forelands which is from time to time flooded by water from the Rhine. The second sample was collected in an area consisting of reed banks, old and recent river deposits, creeks and streams ; this soil consists of clay/sand mixtures or almost only organic matter. A third sampling site was choosen outside the delta, a sandy soil never flooded used as a reference. The $^{239-240}$Pu content of the upper soil layer from the first site has a somewhat higher Pu content than that from the third one (500 mBq/kg versus 300 mBq/kg, 0-5 cm layer). Pu content decreases with depth in both samples but the differences between the soils remains. The values for the second site are slightly higher than for the first one ; Pu is also observed at greater depth and considerable enrichment seems to occur.

2.3. Bioaccumulation

Laboratory studies on the behaviour of the long-lived radionuclides in a marine environment were conducted by the CNEN (Fiascherino, I). In collaboration with the IAEA (Monaco) laboratory, experiments on accumulation, distribution and release of Tc by marine organisms were conducted with the ^{99}Tc beta-emitting isotope and ^{95m}Tc gamma-emitting nuclide particularly suitable for experiments on accumulation. Possible interaction of pertechnetate (TcO_4^-, the most stable chemical form of technetium in aqueous environment) with naturally occuring polymers and biological macromolecules were studied. Pertechnetate reduction needs strong reducing agents but of particular interest is the reaction of pertechnetate with amino-acid cysteine. It was shown that several phytoplanctonic species do not accumulate technetium to any appreciate extent.

Accumulation of Tc from seawater and from contaminated food (Artemia salina) by the shrimp Palaemon elegans was also studied. The

radioactivity in both cases was almost entirely localized in the hepatopancreas but the kinetics of elimination were somewhat different. These observations suggest that in the hepatopancreas of Palaemon elegans the Tc could be transformed to less mobile chemical forms. The metabolic conversion does not occur when the isotope is accumulated from food, probably because the Tc is previously metabolized by Artemia.

Studies on the biological availability of transuranium nuclides have been concentrated on food species eaten directly by man (MAFF, Lowestoft, UK). Concentrations of Pu, Am and Cm were followed in the Irish sea and the dose to man resulting from alpha-emitters in general in a variety of fish species has been evaluated. The consumption of fish can be considered to be of minor importance relative to the shellfish pathway and to the crustacean one. The occurence of ^{237}Np in marine biological materials in the Windscale area has also been demonstrated and analyses of U, Th (and ^{210}Po) has been done in a variety of organisms to estimate their relative importance as a source of radiation both to man and to marine organisms (MAFF, Lowestoft, UK). The inventory of $^{239-240}Pu$ in biomass of brittlestars (benthos) at Thule (Risø Nat. Lab., Roskilde, DK) was determined in 1974 (28 MBq) and in 1979 (22 MBq), the corresponding effective half-life is of approximately 16 years. Shells of bivalves were analysed for $^{239-240}Pu$ and ^{241}Am. The mean ratio $^{241}Am/^{239-240}Pu$ was 0,2 i.e. between that of fallout (0,3) and accident debris (0,1). The inventory of bivalves was estimated at 250 MBq in 1979 as compared to 300 MBq in 1974 corresponding to a half-life of approximately 17 years.

The direct impact of a nuclear power plant wastes on a representative freshwater ecosystem (Meuse) was studied at the site of Tihange (IHE, Bruxelles, B). Contrary to the shellfish, fish concentrate ^{137}Cs, ^{60}Co and ^{54}Mn in decreasing order in their tissues, ^{137}Cs is localized mainly in spleen and gonads. Among the different species, the highest level of ^{137}Cs was found in the perch, a secondary or even tertiary consumer. Kinetics of accumulation of ^{134}Cs, ^{58}Co and ^{99}Tc by the algae Scenedesmus obliquus (a test algae of the Meuse phytoplancton and one of the first links in the fresh water food chain) was established in relation to time concentration and presence of chelating agents (Univ.

Louvain, B). ^{134}Cs and ^{60}Co absorption was a function of the specific activity and was rapid during the first hour. Tc absorption was almost complete after one hour : concentration factors are related to the concentration used (0,31 - 10 μCi/l* / 0,01 - 0,6 mg/l) and decrease with the increase of Tc concentration (50-20 ; dry weight).

3. TERRESTRIAL ENVIRONMENT

3.1. Soil accumulation of radionuclides.

Models were derived from field data and laboratory column experiments (ITAL, Wageningen, NL) to predict the behaviour of ^{137}Cs and $^{238,239,240}Pu$ in soil of Western Europe ; at the same time methods of determination of ^{137}Cs, ^{238}Pu and $^{239,240}Pu$ in soil were developed. There are considerable differences in the degree of sophistication of the models for Cs and Pu both derived from a ^{90}Sr model previously established. The ^{90}Sr model is a simulation one, while a pseudo-residence time model was applied to Cs and Pu. The prediction of irreversible absorption/desorption phenomena was a major difficulty in establishing these models. The ^{90}Sr model was confirmed by other theories, meanwhile less data are available for ^{137}Cs and few observations were devoted to $^{239,240}Pu$. Moreover, a study of the Pu chemistry shows that so many complications may occur, that it must be assumed that, in numerous situations, the existing model will not be applicable (long term behaviour of Pu in soils).

The mobility of transuranium nuclides and specially of Pu, originating from irrigation water was also determined (C.E.N., Cadarache, F). A fraction of 1 to 10% is soluble in the water used and may migrate in soil.

Behaviour of tritium in soil was considered (C.E.N., Mol, B) in a general project devoted to the tritium contamination in temperate regions. The distribution of tritium in soil, following a single contamination, shows the following trend : accumulation in the upper layer (0-10cm) a few hours after the deposit ; a decrease of this concentration of 100 times one month later and an accumulation in deeper

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* 1 μCi = $2{,}710^5$ Bq

layers ; 0,3 % only is present in the upper layer 39 days after the contamination.

3.2. Availability for plants

In the Rhine-Meuse-Scheldt delta, analyses of Pu has been realized on a few vegetation samples (I.T.A.L., Wageningen, NL). In Aster tripolium (a salt-marsh plant) the ratio $^{238}Pu/^{239}Pu$ is higher (0,14-0,27) than the values found in salt marsh sediments (0,08-0,14). The concentration of Pu and Cs in this plant appear to be very low in comparison to grass samples harvested in two French areas located respectively in North Cotentin and next to La Hague ; the highest concentration of the last sample (one order of magnitude) is thought to be due to the atmospheric recycling of marine aerosols.

In soils the presence of organic compounds increases the complexation and mobility of the transuranium nuclides and modifies their transfer factor from soil to plant (C.E.N. Cadarache, F). Moreover the activity deposited also influences this transfer : it is lower in highly contaminated soil conditions and higher where the deposit is low. The deposit in soil is thus an important factor in the transfer of transuranium nuclides from soil to plant, this phenomenon is due to the physico-chemical evolution in the soil and a rapid migration of complexed and pseudo-soluble forms.

Kinetics of tritium and C-14 incorporation in green algae were studied under stationary conditions and under continuous flow growth conditions with single injection and in single or chronic contamination situations (Bundesgesundheitsamt, Berlin, D). The level of balance that is achieved after repeated incorporations in the biomass corresponds with models generally observed in pharmacological studies (Bateman function).

Studies on tritium were conducted on various plant species (beet, potato, peas, carrot) contaminated with a single dose deposit of THO simulating in that way an accidental release (C.E.N., Fontenay-aux-Roses, F). The ratio of the specific activity in organic material and in tissue water was measured during the contamination period until harvesting. This ratio varies from 5,2 ($pCi^{3}H/gH$) in the seeds of pea plants to 0,84 in potato tuber. A good correlation was

found between water tritium content of superficial soil (0-10 cm) and tritium content of tissue water of the shoots of plants studied.

Plant and soil factors governing iodine uptake from soil and soil-solution were studied by the Royal Vet. and Agric. Univ. (Copenhagen, DK). The aim of this project was to verify if the rate of iodide and iodate uptake by intact plants from nutrient solution of approximately the same composition as the soil solution of a fertile agricultural soil depend upon the following factors : a) the area of the active root surface, b) the concentration of iodine in the soil solution at active root surface, and c) the conductivity of active root surface. On Barley grown in a growth chamber in water culture, iodine net uptake rate per unit of root length was related to the concentration of iodide in solution by a Michaelis-Menten type relation. The parameters of this relation are a function of the pH-value of the nutrient solution. The net uptake rate of iodide per unit of root length decreases, even at constant iodine concentration with increasing pH of the nutrient solution ; in some pH conditions, iodide concentrations in solutions were found below which no uptake of iodide by plants occurs. A similar experiment was realized on ryegrass cultivated in pots containing soil treated with iodide. Iodide accumulation by aerial parts of ryegrass could be expressed by an equation of the Michaelis-Menten type, as in root uptake experiments. A model describing iodine (and ^{129}I) uptake by plants from soil should only incorporate parameters related to those chemical species of iodine in the soil solution which contribute significantly to iodine uptake via the root system. According to some authors, small iodinated organic molecules are present in soil solution, and may, in addition to iodide, be taken up by plant roots. Actual results show that reliable values of iodide uptake parameters can be obtained from solution culture experiments. The importance of iodide (^{129}I) relative to other chemical forms of iodine in uptake must be determined by further plant uptake experiments realized in soil.

Another approach of uptake mechanisms by plants was realized with technetium on soybean plants cultivated in nutrient solution and on peas growing in pot containing contaminated soil (Univ. Louvain, B). Accumulation factors of technetium (TcO_4^- in the medium) in aerial parts of plants are very high, as high as for some nutrient elements. The Tc transfer factors observed in nutrient solution and controlled conditions

for soybean are 20 times higher in leaves than in roots. The analysis of the plant sap showed that ^{99}Tc was mostly of the TcO_4^- form (the available chemical form for the plant) which explains its very high mobility in the plant. In the leaves, according to the reducing power of the cell, most of the Tc ($\pm$ 80 %) is bound to some molecule of M.W. which range from 4.000 to 10.000. Kinetic uptake studies showed that the uptake mechanism is an energy requiring one, i.e. that transfer of TcO_4^- molecule through the cell membrane is an active transport. Translocation of TcO_4^- from root to leaves is following the same kinetic law as uptake by root from nutrient solution, both phenomena are well described by a multiphasic-type curve.

Transfer of ^{99}Tc from soil to plant was studied with pea plants grown on seven typical soils contaminated with different levels of ^{99}Tc. The translocation of technetium from soil to plant leaves is high, but its transfer is reduced in soils rich in organic matter or poorly drained. Availability of Tc for plants is depending on characteristics of the soil which may be responsible for some chemical transformation of the pertechnetate.

Root and foliar uptake of radioactive contaminants by crops ; their transport and redistribution in different plant organs were studied in I.T.A.L. (Wageningen, NL) ; experiments have been performed with plants growing on nutrient solutions and in soils. The ^{54}Mn, ^{60}Co and ^{65}Zn transfer has been studied. Large differences among the three radioisotope transfers were observed with a clear dependance on the age of the plants. Zn is strongly bound with almost no redistribution and with very slow isotopic exchange rates. Comparative transfer studies of different radionuclides (^{60}Co, ^{65}Zn, ^{59}Fe, ^{54}Mn, ^{90}Sr, ^{134}Cs) were performed with several plants species growing on a sandy-loam soil. The transfer coefficients of the divalent cations with the exception of iron are rather high, being on average higher than that of the monovalent cation Cs.

The availability of radiocontaminants may be reduced to a certain extent by the use of some synthetic ligands (I.T.A.L., Wageningen, Nl). A polyamine-type ligand, tetraethylene-pentamine (tetren) forms stable complexes with some transition metals to which some radiocontaminants belong. In this study several well defined West-European soils were

used. The stability of the tetren complexes is higher than the stability of the metal-humus complexes. Tetren complex formation results, in nutrient solution, to a marked decrease of the Cu-absorption by the maize roots (Cu enters the root system as a Cu-tetren complex) and to a higher translocation of this element. Application of tetren on a heavy clay soil contaminated with copper results in a diminution of the metal toxicity (yield). These results demonstrate the very beneficial effect of tetren at toxic concentrations of transition metals (e.g. Cu, Co, Zn) whereas no deficiency symptoms occur at trace levels. In cases of local contamination, complexing agents of the polyamine type (e.g. tetren plus clay mineral) may be used as a strong "temporary sink" for stabilizing the situation and complexing agents may be used to reduce the soil-plant transfer without provoking nutrient deficiencies.

3.3. Long-term transformation of nuclides in soils.

Microorganisms may take up, metabolize and excrete the waste radionuclides in the environment. As well as in water as in soil, such processes may modify the availability, the transfer factors and the toxicity of radionuclides for plants and animals.

The long-term behaviour of transuranium nuclides (^{239}Pu, ^{237}Np, ^{241}Am, ^{244}Cm) in soil was studied in controlled conditions (C.E.A, C.E.N., Cadarache, F). Pu "aging" is responsible for an increase of the soil-plant transfer factor (10^2 times). These modifications were probably due to microbial solubilization, complexation by bioproducts, migration of soluble forms and in some cases to some fertilizing effects (biogeochemistry).

Mineralization of organic compounds due to microbial processes may modify, in the long-term, the bioavailability of the isotopes to plants. The fraction of transuranium nuclides present in soil which is incorporated in organic matter (fulvic-humic acids) after four years is 20 to 30 times higher than the available fraction. Np availability for plants is higher than those observed for the other transuranium nuclides.

Moreover, it has been observed that interactions may occur between the different transuranium nuclides, due on the one hand to the specific

activity of the isotopes and on the other hand to their redox potentials. Moreover, the uranium-thorium matrix accompaning wastes may partially modify the soil-plant transfer. These results emphasize the importance of studies considering the behaviour of transuranium nuclides in soil as a bulk and not taken individually. It must be stressed that such a situation could correspond to the real situation as far as nuclear plant released materials or storage of wastes are concerned.

The aging problem of technetium was also investigated (Univ. Louvain, B) ; after three successive cultures the transfer factor of Tc from soil to pea plants was reduced and its relative distribution in the plant modified. These results indicate some modification of the technetium chemical form in soils with time and the problem requires more study.

3.4. Toxicological Aspects.

Some microorganisms are responsible for very important biological functions in soils or in living organisms. Via microorganisms metabolism, radionuclides may severely affect some biological functions in plants and animals.

It has been observed (Univ. Louvain, B) that Tc (10^{-1} ppm) has a negative effect on the N_2 fixation process by two microorganisms Rhizobium japonicum (in microaerobic conditions) and Azotobacter chroococcum (fixation of N_2 in presence of O_2) ; the mechanisms remain to be elucidated. Accumulation of Tc was only observed in the cells where N_2 fixation occurs (heterocystes of Anabaena Cylindrica) and its growth is severely reduced in a growth medium free of combined nitrogen ; some supply of organic nitrogen decreases the toxicity symptoms.

Recent experiments have also shown that Tc influences the normal growth of plants at relatively low concentrations. The toxicity level varies with the age of plants (soybean) (Univ. Louvain, B) and in addition to a change in the phenology of the leaves (spinach), pertechnetate appears to hamper the normal fluorescence of intact growing spinach leaves possibly by inhibition of the photolysis of water (I.T.A.L. Wageningen, NL).

Possible interactions of TcO_4^- with naturally occuring polymers, biological macromolecules and with the amino-acid cysteine (C.E.N.,

Fiascherino, I ; C.E.A.-C.E.N. Cadarache, F) are of great interest to understand the effect of technetium on biochemical reactions.

3.5. Metabolization of radionuclides by animals.

The metabolism of tritium in farms animals (mammals) has been studied after administration of tritium in a single dose or in chronic uptake experiments. Tritium was given as tritiated water and organically bound tritium (C.E.N./S.C.K., Mol, B ; Landbouw Hogeschool, Wageningen, NL). The biological half-life of tritium in the body water pool has been determined in different species. Much attention has been paid to the incorporation of tritium into organic constituents, both in the organisms and in the secretions of the animals.

In pigs having ingested tritiated water regularly during the entire pregnancy and for 43 days thereafter, organically bound tritium in organs reaches an equilibrium value of about 11 % of that of the tritiated water ingested (C.E.N./S.C.K., Mol, B). Only brain has a significantly greater specific activity (17 %). Turnover of organic tritium varies among organs, it is slowest in brain, followed by muscular tissues, and the most rapid in liver and in intestine. Serum proteins have about the same turnover and the same equilibrium value as organs. From these turnover values, one can estimate that continuous ingestion of tritiated water during pregnancy results in a dose from organic tritium which, in most organs, is only about one third of that due to tritiated water alone. In brain, this dose from organic tritium may, however, be as large as or even slightly exceed that from tritiated water.

The metabolism of tritium has also been studied in lactating cows after administration of tritiated water and organically bound tritium (Landbouw Hogeschool, Wageningen, NL).

Special attention was given to the organic constituents of milk (casein, lactose, milk fat). It has been observed that the incorporation of tritium in milk constituents was different if tritium was administered to the cow as tritiated water or as tritiated corn or hay. In conditions of chronic intake of tritiated water, about 1,6 % of the daily ingested tritium is secreted in each litre of milk ; of this no

more than 5 % is organically bound, the remaining 95 % being found in milk water. In organic compounds : the highest concentration is found in milk fat, closely followed by lactose ; the casein content reaches half of the lactose value. From these observations it follows that the dose to man which results from milk from cows which have been drinking tritiated water comes predominantly from the tritiated water of milk.

After ingestion of tritiated corn by the cow, milk fat was found to have the highest specific activity followed by milk water. The specific activity of casein and lactose were similar (60 % of the value found for milk fat). Due to the high water content of milk (about 87 %) the dose to man, also in this case, will derive primarily from ingested tritiated water.

After ingestion of tritiated hay, the highest tritium concentration was again found in milk fat reaching 2,5 times the concentration in casein and about 16 times that in lactose. The tritium concentration in milk water was low and comparable to that in lactose. The transfer of the daily ingested tritium, secreted per litre of milk, can be estimated to range between 1,0-1,5 %. More than half the tritium is found in milk water on a per litre basis and about one third in milk fat.

Moreover, it was also found that, dependent on feeding, a varying incorporation of tritium in milk casein takes place (Bundesgesundheitsamt, Berlin, D) : the tritium distribution in the different aminoacid components of casein differs strongly with tritium origin.

A stocktaking of iodine-129 in the thyroids of pasture animals was made for samples collected in selected sites of the European Communities where reprocessing plants are planned or already in operation (G.S.G., Hannover, D). The iodine-129 concentrations, measured in some countries of the European Communities, are generally in the same range as those measured in the U.S.A. with cattle and humans. Nevertheless, the highest concentrations observed in certain areas, e.g. around Mol in Belgium may be due to the spent fuel which has been reprocessed. ^{129}I levels above the mean value may thus be expected in the near vicinity of such plants and can be observed several years after shut down of the plant.

4. ATMOSPHERIC ENVIRONMENT

4.1. Dispersion in the atmosphere.

The general problem of the radioactive releases and their dispersion in the atmosphere following a hypothetical reactor accident was discussed (C.E.C. Seminar, Roskilde, 22-25 April 1980) and the following problems developed : characteristics of accidental releases ; atmospheric phenomena influences ; characteristics of deposition. Short, intermediate and mesoscale range models of dispersion were proposed.

The ^{85}Kr released in the atmosphere by the reprocessing plants was monitored (Rijksuniversiteit, Gent, B). During the period 1979-1980 a slight increase of the ^{85}Kr concentration occurred in the experimental zone. A programme was elaborated for drawing contourlines on the map for given concentration levels and for plotting the time profile of the concentration. Secondly a statistical analysis of the frequency of the peak concentrations has been performed. And finally the evaluation of the presumed synergistic effect of U.V. and low level ionizing radiations on the formation of aerosols (SO_2 to H_2SO_4 transformation and accelerated nucleation) were investigated using a flow reactor.

4.2. Physical resuspension.

4.2.1. Resuspension from seawater

Low-level radioactive wastes discharged to coastal waters from nuclear installation have been identified as the major route by which radioactivity might be released to the environment. Mechanisms for returning even a small fraction of the radioactive burden of this offshore water to the land must thus require consideration. Sea spray, or the aerosol resulting from its evaporation, is a possible vehicle for this material. Laboratory experiments (AERE, Harwell, UK) demonstrated : a) that plutonium may be substantially enriched in both the surface of sea water and in the aerosol generated by bubbling air through the water and b) that tetravalent and hexavalent plutonium is enriched in seaspray by one or two orders of magnitude relative to sodium. These observations suggest that a similar effect may be

anticipated in the environment, and should be taken into account when acceptable norms of discharge to sea are considered.

On the other hand, analysis of soil samples of the coastal region of Cumbria has shown that the radioactive deposit cannot only be explained by nuclear weapon fallout. The anomalous Pu content of the soil samples and its inland distribution confirm a significant contribution from the seaward direction (A.E.R.E., Harwell, U.K.).

4.2.2. Resuspension from land surfaces.

Resuspension from land surfaces by the wind was studied in controlled conditions using a wind tunnel set up on grassland or on a bare soil contaminated with suitable tracers (AERE, Harwell, UK).

The variation of the resuspension rate with wind-speed, particle size, vegetation cover and moisture content of the soil was investigated. It was found that changes in wind speed and in the duration of weathering by the wind caused most of the variation in resuspension. The resuspension rate decreased in proportion to the reciprocal of weathering time and increased with the wind speed to the third or fourth power (results concerning sub-micron particles). No consistent pattern of variation with moisture content of air or soil was apparent, and the difference between bare soil and grass covered soil did not exceed a factor of three.

Raindrops can disperse particles from the surface of dry, or of very wet soil and from grass bades and resuspension in the field could include contributions due to rain splash and traffic as well as the wind. For deposits as old as weapons fallout trace element measurements show that the resuspension factor due to all causes cannot exceed 7.10^{-11} m^{-1} on average in Great Britain.

Tritiated water vapour is exchanged between atmosphere and terrestrial surfaces at a significant rate. Close to the source of a short release this exchange may result in more rapid deposition than a moderate rainfall. The behaviour of the HTO during dry spells can be described by a simple diffusion model, which should allow calculation of the doses resulting from a short release of HTO. Rain displaces the HTO deeper in the soil, and short grass modifies the rate of return to the

environment. These data were obtained in controlled conditions (wind tunnel in laboratory) and in the field (A.E.R.E. Harwell, U.K.).

4.3. Atmosphere - plant exchanges.

Transfer of tritiated water vapor between atmosphere and plant (C.E.A., C.E.N., Fontenay-aux-Roses, F) was investigated in the field (Vitis vinifera, Zea mays and Solanum tuberosum) and kinetic studies were done in relation to the temperature and stomatic resistance. Tritiated water exchange between atmosphere and leaves, which is a gaseous exchange, increases when stomata opening and traspiration rate increase. Uptake and also loss of tritiated water by plants are more rapid during the day than during the night and more rapid in spring than in autumn. On the basis of these observations a model was developed giving the concentration of tritium in water of leaves versus time, knowing the temperature and the stomatal resistance. This model allows an evaluation of the concentration reached at equilibrium and the biological half-life of tritium present in tissue water. Rate of incorporation of tritium in relation to photosynthesis and determination of its distribution in the plant following a gaseous contamination are actually studied on two plant species (potato and maize) differing in their photosynthetic system (C-3 and C-4 plants).

The results obtained in Great Britain (A.E.R.E., Harwell, U.K.) using bean leaves (wind tunnel) are in good agreement with the model established.

Experiments with tracers have shown that plants are capable of releasing a small fraction of the total amount of heavy metals absorbed by the roots from the foliage. An experiment (Univ. Louvain, B) was designed to study the role of volatile exudates in the transfer of different radionuclides. No significant contamination of the air was detected from different species cultivated in contaminated nutrient solution or soil (^{65}Zn, ^{134}Cs and ^{99}Tc).

Leachability of technetium by rains from foliage of contaminated plants was also established (1 to 13 % of ^{99}Tc content of the aerial part, after 36 h depending on species and contamination levels). The predominant form of Tc leached was the same as that present in nutrient

solution (TcO_4^-) ; nevertheless a small quantity of Tc leached is modified and some cationic forms were observed in the leachates in an increasing percentage with the duration of rain (6 % after the first hour to 15 % after 36 hours).

5. EVALUATION OF DOSES TO MAN

5.1. Expression of the transfers.

Experiments conducted in controlled conditions aiming at the determination of transfer coefficient and redistribution of some radiocontaminants in plants, have shown that the commonly used expression transfer coefficient or concentration ratio is misleading (I.T.A.L., Wageningen, NL). Indeed, great differences in the transfer of radioisotopes were found to depend on : the age of the plants, the stable isotope concentration (^{65}Zn...), the degree of maturation at harvest time... It was suggested that the transfer of radionuclides between the "acceptor" and the "donor" is not characterized by a constant ratio. The term transfer coefficient is only valuable for "average conditions" within the ecosystem. The transfer of a radiocontaminant from one compartment to another could only be described by a "transfer function" which characterizes the accumulation of the radiocontaminant in the acceptor in a dynamic way.

Research work has shown that variations in the transfer coefficient obtained in defined conditions may be due to : a) time (aging) : for transuranium nuclides, mineralization of organic compounds via microorganisms may, over a long-term period, produce nuclides directly available for plants (C.E.A., C.E.N., Cadarache, F) ; technetium availability for plants decreases with time due to mineralisation and probably to microorganism metabolization (Univ. Louvain, B) ; b) source of pollution : according to the mode of feeding either as tritiated water of as tritium labelled hay, a varying distribution of tritium in milk components takes place (C.E.N. Mol, B) ; c) premetabolization of radionuclides : uptake of radioactivity by water organisms from water or food modifies the localization and the desorption of technetium (C.N.E.N. Fiascherino, I) ; d) concentration : transfer of Pu isotopes from soil to plant varies with contamination level : the higher is the

activity deposited, the lower is the transfer coefficient (C.E.A., C.E.N., Cadarache, F) ; e) presence of other pollutants : Tc uptake by plants from contaminated solution decreases if plants had previously accumulated Cd (relative stability of complexes formed by Cd and Tc) (Univ. Louvain, B); some synergistic effect was observed in the soil-plant transfer when several actinides were present in the soil and when the nuclides were released in uranium-thorium matrix (C.E.A., C.E.N., Cadarache, F). In an area polluted with fuel oil due to the "Amoco Cadiz" accident abnormally high levels of ^{144}Ce were found (particulate nature of ^{144}Ce and mechanical action (Univ. Nantes, F) ; f) Species : as an example, it can be mentioned that laboratory (C.N.E.N. Fiascherino, I) and field investigations (M.A.F.F. Lowestoft, UK) have shown that concentration factors for Tc in marine brown algae can be three orders of magnitude higher than those determined in several species of green algae.

5.2. Transfer of tritium.

Information on the residence time, pattern of movement and distribution of tritium in typical ecosystems, its incorporation into biological compounds and its transfer along food chains have been collected by several Research Institutes.

Incorporated tritium is rapidly distributed into organisms first to the body water and with a certain delay to the organic components. While ingested tritiated water is quite rapidly eliminated (biological half life in man : 10 days), organically bound tritium, when present in food, remains in the organisms for a longer period of time.

Studies on transfer of tritium given as tritiated water or food were carried out on livestock (C.E.N. Mol, B). Such a study revealed that contamination level from organic tritium is probably not more than 1,5 times greater than that from tritiated water. In other investigations in which tritiated water was given to pigs during the entire pregnancy it was confirmed that the additional contamination due to the formation of tritiated organic molecules is not very high.

In a joint project, French, Belgian and Dutch laboratories (C.E.A., Fontenay-aux-Roses, F ; C.E.N., Mol, B ; Landbouwhogeschool, Wageningen,

NL) investigated the transfer of tritium and more specially : the relationship between environmental contamination rates and some seasonal production in the Mediterranean region and in a humid temperate climate ; the transfer process in the food chain : water - fodder - bovines - dairy produce and the role of each species.

The distribution of tritium and carbon-14 and their compounds in the aqueous and organic phases of various steps of aquatic and terrestrial food chains has been investigated by the Bundegesundheitsamt (Berlin, D). The experimental investigations intended to follow the tritium and the ^{14}C on the one hand in phytoplankton (green algae), zooplankton (daphnia), fish, and on the other hand in plants, cow and man. In these organisms, incorporation of the nuclides was followed in proteins.

The quantitative behaviour, as for as distribution and dose received are concerned, has been assessed in a mathematical model. The available hydrogen is divided into three compartments : 67 % which exists as water and is eliminated with a biological half-life of 10 days, 3 % which has a biological half-life of 30 days and the last fraction which is more firmly bound and exchangeable with tritium in water to a limited extent, has a biological half-life of 350 days.

In addition, the size and conversion rate of compartments within the food chains have been determined in order to arrive at the necessary total balance for the assessment of radiation exposure to man by tritium and ^{14}C.

6. CONTROL OF CONTAMINATED AREA

In the I.T.A.L. (Wageningen, NL) laboratories, the agricultural measures required to reduce radiation doses to man caused by a severe nuclear accident were determined. Based on actual models, to calculate radiation doses to man from deposited radionuclides via the agricultural pathway, possible measures were described and their limitations and practicability determined.

These measures can be advised depending on the degree of contamination and the estimated radiation doses to man. Some to them are of short-term and others of long-term but all of them could be improved essentially in their practicability by : improvement of transfer

models ; determination of realistic parameters to be used in these models ; study of more efficient methods to measure contamination levels in the field ; study of the effects of application of some complexing agents to soils or cattle to reduce the transfer of radionuclides ; study of product treatments which reduce the radionuclide content of the final product...

7. CONVENTIONAL POLLUTION DUE TO NUCLEAR POWER PLANT

The thermal impact of a nuclear power plant (P.W.R. type), Tihange 1, on macroinvertebrates and fish living in the river Meuse was studied by the Univ. Namur and by the I.H.E. (Bruxelles, B). The water temperature of the Meuse was continuously recorded upstream and downstream of the nuclear power plant. The thermal differences between the two parts of the river are very small during the winter, increase in spring and reach 3 to 4°C in summer and autumn (Univ. Namur, B). Investigations on aquatic invertebrate populations showed that molluscan bivalve Dreissena polymorpha, and shrimp Atyaephyna desmareti which were living at the lower sampling site seemed to grow at a higher rate during Spring. Furthermore, artificial water heating appeared to extend the growing season beyond October. On fish population, thermal elevation of water seems to have no noticeable effect from a qualitative point of view. The thermal discharges slightly influence the gonadosomatic relationships of the roach. Such differences observed between the upper and lower sampling sites are comparable with natural changes between two isolated populations.

The biocide (Na hypochlorite) used in the refrigeration circuit of the nuclear plant to avoid algal development, was tested in laboratory experiments and in situ (I.H.E., Bruxelles, B). On fishes, some asphyxiation symptoms were observed (0,22 ppm, 15 min.) ; on bryophytes the photosynthetic activity was decreased from 15 to 20% after the chlorination (mesured 24h after the end of treatment). Similar effects were observed in laboratory studies in which influence of chlorine doses, temperature, algae concentrations, period of treatment were investigated and readjustment time determined.

8. RELEASE OF RADIONUCLIDES BY NON NUCLEAR PLANTS.

A review of the recent data on "Health and environmental impacts of energy sources involving radioactivity (C.E.N. Mol, B) indicates that with the present technology and based on an equivalent production of energy, the coal-fired plants have the potential for a higher radiologic impact on the population than nuclear power plants. Radionuclides potentially hazardous to human health and ecosystems which are present in coal are ^{235}U, ^{238}U, ^{232}Th, ^{228}Th and associated daughter products. The radionuclides can also enter the environment prior to coal combustion through runoff from mining-operations. Additional research is necessary concerning the concentration of naturally occurring radionuclides of various types of coal obtained from various geographical locations.

Most phosphate fertilizers contain the natural radionuclides of the uranium series as well as potassium-40 in specific activities appreciably exceeding the average specific activities found in common soils. Results of one study (cf. Seminar on the radiological burden of man from natural radioactivity in the countries of the European Communities, Le Vesinet, 4-6 Dec. 1979) show that radionuclides contained in fertilizers contribute very little to the external radiation exposure of the population even if complete retention of radium deposited with fertilizers in the soil during the last 80 years is assumed. In contrast, the occupational external exposure of individuals due to phosphate fertilizers may reach values up to about 50 mrem/y* (50 % increase of the natural radiation exposure). Furthermore, the internal radiation exposure of persons working in fertilizer storehouses or in production plants has to be considered.

9. GENERAL CONSIDERATIONS.

Although many data have already been accumulated on the behaviour of several radionuclides, the information available is not sufficient to provide a solid scientific basis for the assessment of potential exposures liable to occur from the operations related to the whole cycle

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* 1 mSv = 10 mrem

of nuclear fuel (mining, milling, fuel fabrication, reactor operation, fuel reprocessing, waste disposal).

The new principles of radiation protection require as input data for proper evaluation of collective dose committment a detailed knowledge of the behaviour of radionuclides in the environment and their transfer through food chains. This is especially true in relation to the longer lived radionuclides and their significance for human radiation exposure over long periods of time.

For that reason, most of the research carried out in the last years has been concerned with transuranic and other long-lived radionuclides, such as ^{99}Tc and ^{129}I. Relevant information has been acquired on their behaviour in terrestrial and aquatic environments, as well as their transfer through the food chains.

However, several gaps remain and the processes of dispersion, reconcentration and transfer cannot be fully understood. An evident case regards technetium for which recent experimental data suggest that the uptake of its isotope ^{99}Tc by vegetation from soil may be two or three orders of magnitude higher than the value currently being used in radiological assessments. This implies that the dose delivered to man through the transport of ^{99}Tc via food chain pathways is higher than previously assessed. Therefore, the results of short-term laboratory experiments cannot be extrapolated to real situations. On the other hand, mathematical models, usually based on thermodynamic data and solubility equilibria, are not sufficient for a satisfactory description of the behaviour of long-lived radionuclides : in many cases, kinetic aspects may be very important in determining the initial distribution of radionuclides.

In the next future, a better knowledge of the biogeochemistry of such elements should be of great help in the interpretation of field investigations and in programming experiments under strictly controlled conditions. A correct equilibrium between "in situ" and laboratory studies is needed to acquire a better understanding of the processes responsible for the environmental behaviour of radionuclides.

On the basis of such knowledge, obtained by extensive radioecological investigations, the radiation protection could be provided with a solid scientific background for the assessment of the dose arising from any given discharge of radionuclides into the environment.

SECTOR C

SHORT TERM EFFECTS OF IONIZING RADIATION

1. PRIMARY EFFECTS OF IONIZING RADIATIONS ON NUCLEIC ACIDS

1.1. Purpose and general view

When a living system is subjected to ionizing radiations, the energy transferred to its constituent molecules is large enough to disrupt atomic orbitals and eject electrons. This initiates a series of extremely fast molecular reactions involving free radical intermediates and causing the system to move into a new thermodynamic equilibrium state in which some of the original molecules are irreversibly transformed into chemically stable radiation products. The whole series of interconnected events developing between the initial energy absorption and the formation of these radiation products is conventionally called "Primary Effects". Although it is impossible to accurately define the upward boundary of this interval of time, it is of the order of seconds. Thus of the long sequence of biological events in the irradiated organism, (mutation, cancer, death,) the primary effects occupy an extremely short and crucial time period during which the eventual chemical modification of the genome of the organism is decided. An elucidation of the intricate phenomena taking place during the primary effects phase constitutes the molecular clue for an understanding of the mechanisms of radiation action and hence for possible control of their final effects.

Nine laboratories were engaged in the execution of the programme on Primary Effects. It is worth noticing that all the project leaders and their staffs belong to the "European Group for the Study of Primary Effects on Nucleic Acids". This group arose ten years ago under the aegis of the Commission with the object of facilitating the exchange of ideas and information between european scientists working in this

5)

field. This idea materialized into the formation of mixed teams, where physicsts, chemists and biologists started working concertedly on a same problem but from different viewpoints. The Group on Primary Effects is presently established as a genuinely interdisciplinar research team, also enjoying the active participation of several european scientists from outside the community countries.

1.2. Free radical intermediates

Free radicals are paramagnetic, unstable species, precursors of the chemically stable radiation products. The free radical stage is crucial in radiation protection : firstly because it is the earliest phase which can be analysed by means of well-developed experimental techniques and, secondly, because at this early stage the sequence of events which would normally lead to radiation damage can still be interrupted or diverted towards less vital targets than the nucleic acid macromolecules. The study of radiation induced free radical structures and the study of conversion reactions transforming primary radicals into secondary radicals is the central object of physicochemical investigations performed mainly by physicists using the Electron Spin Resonance spectroscopy.

DNA- located free radicals can be divided into two classes : those produced by the direct action of the radiation (direct effects) and those formed via the chemical attack of other radicals previously formed in the aqueous environment (indirect effects). Whilst in in vivo conditions both effects are thought to cooperate in the DNA damage, in vitro they can be investigated in isolation. Investigations on the two radicals classes were performed at the Free University of Brussels and at the University of Regensburg.

1.2.1. DNA radicals formed in conditions of prominent direct effects

The methodological approach followed by the group working at the University of Brussels during the period 1976-1980 may be summarized as follows :

a) The complexity of the systems studied was progressively increased from the individual nucleotides, through nucleotide complexes possessing only part of the DNA structure to the DNA molecule itself.

b) To selectively study the direct effects of irradiation, the above systems were irradiated in frozen aqueous solution. In the frozen state the solvent-solute phase separation is so drastic that the contribution of indirect effects to the radiolysis of the solute becomes negligible.

c) The study of primary radicals was easily performed at 77°K, since most of these radicals are stabilized at this temperature. On the other hand, since an increase in the temperature of the sample supplies to these primary radicals the activation energy necessary to enter radical-radical conversion reactions, the samples were warmed up slowly to permit an ESR analysis of these reactions "in slow motion".

d) The ESR spectra obtained in radiation research are most often composite, i.e. they result from the superimposition of several elementary patterns. This renders their direct analysis problematic and, in most cases, impossible. A new technique consisting in the computer-assisted processing of this composite spectra was thus developed in Brussels. This technique revealed to be an extremely powerful tool for the identification of the different radicals involved and for the quantitative evaluation of their respective concentrations.

1.2.2. DNA radicals formed in conditions of prominent indirect effects

The project worked out at the University of Regensburg aimed at an elucidation of the molecular mechanisms underlying DNA radiosensitization, in conditions of prominent indirect effects, occurring when the thymine residues are replaced by 5-halouracil. At the molecular level, DNA sensitization and DNA protection are two complementary aspects of a same phenomenon : the possibility of

interfering with the energy degradation pathways in order to modify (enhance or reduce) the final biological effects of radiations. More specifically, the project delt with the study of the reactions of hydrogen atoms (H), electrons (e^-) and oxhydryl radicals (OH), released photolytically or radiolytically from glassy matrices of different nature, with uracil and its 5-methyl- and 5-halogen- substituted bases, nucleosides and nucleotides. The peculiarity of the system chosen lies in the fact that a glassy matrix is solid and transparent. This enabled the group working in Regensburg to carry out detailed analysis of the optical as well as of the paramagnetic properties of free radicals using combined opticaland magnetic resonance spectroscopies as tools of investigation. In this way, the large body of data available from pulse radiolysis studies in aqueous solution (i.e. optical absorption spectra) becomes relatable to the detailed structural informations obtainable by ESR spectroscopy.

Without entering the details of the work performed by the contractant at Regensburg, the following achievements deserve to be underlined :

- In nucleosides and nucleotides, H atoms may react both with the deoxyribose and with the base moiety. In the first case, the results of the reaction will be the formation of C2' and C4' radicals likely to be correlated with DNA strand breaks. In the case of reaction with the base moiety, the preferential site of attack is the C5-C6 double bond.

- Electron reaction only occurs at the bases and is highly diversified : the result of the attachment depends on the pH of the glass, on the tautomeric form of the solute molecule and the 5-substituents. Generally speaking, one can distinguish two classes of anions : π^*-anions and σ^*-anions. The latter ions are thought to be the precursors of halide ion elimination.

The partial results obtained on relatively simple systems like the nucleosides and the nucleotides finally enabled the Group in Regensburg to disclose a possible mechanism for radiation sensitization of DNA by 5-halouracil incorporation. The model starts with electron attachment to

the bromouracil base in DNA. This yields bromide and a uracil-yl radical which initiates a strand break by abstracting a hydrogen atom from a neighbouring deoxyribose.

1.3. Radiation products

The radiation products follows the free radical in time by some fractions of a second. These two steps of the energy degradation process possess substantially different features. The radiation products are no longer paramagnetic. Therefore they lie beyond the horizon of physicists applying ESR techniques. Their domain is that of analytical radiation chemistry, investigated by chemists working mainly with chromatographic techniques. One of the greatest successes of the European Group on Primary Effects was to bring together physicists and chemists and to create the awareness that much collaborative work was to be done in this sector. Two radiation chemical laboratories became particularly involved in this field : the Max Planck Institute in Mülheim and the CEA-CEN in Grenoble. The following is a short review of the most significant achievements, obtained by the two contractants during the period 1976-1980.

1.3.1. Chemical studies of chain breaks

The group working in Mülheim was principally concerned with the study of the physicochemical mechanisms underlying the formation of strand breaks and alkali-labile sites in DNA γ-irradiated in aqueous solution. As mentioned above, in diluted aqueous solution the indirect effects are prominent; in addition one can modify the experimental conditions such that the principal reactive species is the water-released OH radical. In fact, the elucidation of the chemical attack of OH radicals on the sugar moiety of DNA is the achievement obtained at the Max Planck Institute that is highlighted in some details here below.

- OH radicals are rather reactive. Their action at the sugar moiety is, most likely, hydrogen abstraction.

- Because of the high reactivity of OH radicals, hydrogen abstraction will occur more or less at random, i.e. sugar radicals with the free spins at all the sugar carbons will be formed.
- If the hydrogen atom is abstracted from C1', the adjacent base is lost creating an alkali labile site in DNA.
- If the hydrogen atom is abstracted from C2', in the presence of oxygen (this is generally the case under in vivo conditions) an erythrose unit is formed (loss of C1' and base), which is also an alkali labile site.
- A number of reactions can start from the radical at C4', all ending with a strand break.
- A strand break is also the result of hydrogen abstraction from C5' via the breakage of the C4'-C5' bond.

The mechanisms summarized above are a clear example of the fact that some features of the energy degradation process may, in some cases, be elucidated from the very first energy absorption events to the appearance of biological effects. In the present case, the process can sequentially be described as follows :

- Energy deposition occurs mainly in the aqueous phase, thus producing OH radicals;
- OH radicals undergo diffusion-controlled reactions with the sugar moiety of DNA;
- Different types of free radicals are formed, but all of them, via different mechanisms, produce eventually strand breaks;
- The biological effects of strand breaks (if not repaired) is lethality.

1.3.2. Chemical studies on base-located radiation products

While the group in Mülheim was working on DNA strand breaks, at the CEA-CEN in Grenoble another group of radiation chemists worked on a complementary project aiming at an elucidation of the chemical mechanisms leading to base-located radiation products. During the period 1976-1980 this group reached a wide expertise in this field, particularly for thymine and adenine-located products.

An analysis of cytosine and guanine located radiation products is under way of being performed, this permitting the elucidation of the full spectrum of radiation induced products formed when DNA is subjected to ionizing radiations.

According to their results and conclusions, the γ-radiation products at the bases can be divided into two classes : those which are liberated from the DNA during the irradiation and those which remain attached to the DNA chain. Concerning the first class of products, a base can be released intact from the DNA polymeric chain or it can be released broken in smaller chemical products like pyruvamide and urea. Using the modern techniques of analytical chemistry the main DNA released products have been accurately identified.

Probably more important for radiation biology are those radiation products which remain attached to the polynucleotide chain. In some cases, the chemical modification occurring at the bases are such that misreading by the DNA replication enzymes takes place. This leads finally to a modification of the genetic information, i.e. to a mutation. Several products located at the bases thymine and adenine, certainly involved in the further appearance of inheritable mutations have been characterized in Grenoble.

2. SHORT TERM EFFECTS OF IONIZING RADIATIONS

2.1. Purpose and general view

Impairment due to ionizing radiations of the normal activity of both the hemopoietic and the immune systems is to be considered as closely related. Indeed, the different cell lines of these systems have common precursors, originating in the same anatomical sites, and their development is highly interconnected. Twelve research laboratories, during the 1976-1980 period of the last "Biology-Health Protection" programme have performed experimental and clinical studies dealing respectively with :

- hemopoiesis
- effects of irradiation on immune cell populations and their consequences
- bone marrow transplantation.

The overall purpose of these investigations was

1) to increase our knowledge of the effects of ionizing radiations on the hemopoietic and immune system,
2) to improve existing methods and to develop new ones for the evaluation of the consequences of radiation exposure,
3) to study the hemopoietic and immune restoration after exposure to ionizing radiations with or without cell grafts treatment. These studies were carried out at the fundamental as well as at the preclinical or clinical level depending on the knowledge already obtained in the different fields.

2.2. Hemopoiesis

The recovery of both the immune and the hemopoietic systems after exposure to ionizing radiations can be stimulated by drugs or hormones. Thus, the mechanisms regulating kinetics of early hemopoietic precursors under normal conditions or following irradiation have been studied. The group at the university of Naples investigated the influence of erythropoietin and burst enhancing factors (BFU) at the level of the erythroid precursors and showed an important role for BFU on the post irradiation recovery of the erythroid cell line.

This group also reported and increase of BFU in murine serum after irradiation, as well as an enhanced recovery of erythro-and hemopoiesis in mildly irradiated mice following the injection of crude BFU from syngeneic normal mice. One group at the Free university of Brussels studied the catabolism of erythropoietin in marrow aplasia secondary to chemotherapy or X-ray irradiation. This catabolism was unaffected by drug aplasia but reduced after irradiation. Moreover, an inhibitory effect of glucagon on erythropoiesis in mice and rats was demonstrated. Since glucagon acts in most cells by generating intracellular cyclic AMP, it was concluded that pharmacological manipulation of cyclic AMP levels in bone marrow erythropoietic cells may provide new therapeutic tools in the control of hemopoiesis. Another research group at the Free university of Brussels has studied the specific regulation of human hemopoietic stem cell types. Parathormone appears to be a rather specific inhibitor of erythropoiesis. Lactoferrin, a product of mature granulocytes was not inhibitory for granulopoiesis in vitro while peripheral blood lymphocytes were constantly found to inhibit the growth of human colony forming units of the granulomonocytic line.

The group of the university of Ulm studied the normal content of hematopoietic stem cells or progenitor cells in the blood of mice, dogs and humans and its relation to the extravascular stem cell pools. They concluded that the blood granulocytic progenitor cells represent a physiological subpopulation of blood leucocytes and that their concentration is the result of a dynamic equilibrium between immigration from the bone marrow and migration or transformation. On this basis, a number of experimental studies were performed to examine the radiation response pattern of hemopoietic progenitor cells in the blood to single, repeated or low dose rate exposures. The blood stem cells and progenitor cells, in mice and dogs, were found to be much more sensitive to irradiation than other blood cell populations and their changes depended directly on radiation dose. Good preliminary evidence suggests that blood progenitor cell populations may well serve as a useful indicator of whole or partial body radiation exposure. However, further work must be carried out in order to establish the value of these changes to predict early and late radiation consequences.

One group at the Free university of Brussels carried out similar studies in human subjects. They investigated agents that may increase the progenitor cell level in blood and methods of storage and preservation of these cells.

2.3. Effects of irradiation on immune cell populations and their consequences

2.3.1. Immune system

In recent years, the immune system has been shown to be composed by different and interactig cell populations. In the light of these findings, the overall effects of ionizing radiations on the immune system, needed a reevaluation in terms of individual radiosensitivity of the different cell populations in the immune system. The group at the Free university of Brussels analyzed the role of the T suppressor lymphocytes in the isogenic barrier phenomenon and demonstrated that low doses of irradiation could inhibit the normal feedback mechanism of the normal immune response.

By using a cell culture system for the in vitro induction of an immune response in rabbit peripheral blood lymphocytes, two subpopulations of suppressor T lymphocytes have been revealed, differring in radiosensitivity : one radioresistant and histamine binding, the other radiosensitive and without receptor for histamine. These results offer an explanation of the radiation-induced enhancement of antibody response as a direct effect on radiosensitive suppressor cells and rule out an indirect effect on gut epithelium or lymphocyte homing.

The radiation induced enhancement of the immune response has also been studies at the university of Louvain, using a highly thymus-dependent immune response, which had been shown to be strictly controlled by T suppressor cells. After 4 Gy whole body irradiation, enhancement was observed in some rat strains but not in others; it was also observed in F1 hybrids between negative and positive strains. Further studies demonstrated that the genetic control of radiation-induced enhancement was unlinked to the major histocompatibility complex nor was it linked to the light and heavy chain either separately or jointly.

The radiosensitivity of the T helper lymphoid cells was studied by the CNEN group (Casaccia-Roma). They used spleen cells from mice

carrier-primed 4 days before exposure to ionizing radiations and tested them for their ability to help syngeneic normal spleen cells to mount an anti-hapten immune response in vitro after stimulation with the carrier hapten conjugate. The results demonstrated the presence of two helper T cell subpopulations, one sensitive to very low doses of radiations, the other more radioresistant. The physiological role of these subpopulations remains to be determined.

The affinity of the antibodies synthesized after an antigenic stimulations was studied by another group at the Free university of Brussels. They showed that the average affinity of antibodies depends on the control exerted by different T cell populations as characterized by different radiosensitivities, which should be analyzed in further details in the future. These observations are in line with the results of the CNEN group which found antibody affinity up to 20 fold greater in irradiated compared to control mice, when antigen was injected 1-5 days before, or 2 hr-8 wks after a sublethal X-rays dose ranging from 25 to 450 R.

At last, the recovery of T and B lymphoid cell populations after irradiation was measured in an in vitro system by the CNEN group. T-independant and T-dependent immune responses were studied and immune defects could be demonstrated up to three months after a 200 rad irradiation. A complete recovery was found six months after 400 rad exposure. These findings suggest that radiation induced perturbations of the immune homeostasis can eventually recover spontaneously. However, as complete recovery was fully attained only after a long period of time, irradiated individuals are likely to suffer from the late consequences of a long-lasting unbalance of the immune surveillance mechanisms.

Immunodepressive agents which more or less mimic the effects of ionizing radiations were studied in order to get a better insight into the mode of action of such cytotoxic agents on the immunosystem. The group in Milan at the institute "Mario Negri" investigated the action of different cytotoxic agents, chosen as representative of the major classes of immunodepressants, on natural killer cells. Significant heterogeneity exists among cytotoxic drugs in their activity on this type of immune defence mechanism. T suppressor lymphocytes and macrophages were also

used as targets for different immunodepressive drugs. The conclusion of these studies was that cytotoxic agents even when closely related could be substantially heterogenous in their interaction with different populations of immune cells. Such information might be useful for a less empirical application of immunodepressive agents.

2.3.2. Immunostimulatory agents

The "Mario Negri" group in Milan also studied new immunostimulatory agents for the treatment of the immune damage consequent to radiation exposure. Classical agents such as BCG, Corynebacterium parvum, pyran copolymer were shown to have a long lasting effect on T suppressor cells, at variance to what was observed for other compounds like levamisole. K cells were also shown to be important targets of some of these agents. New agents possessing immunostimulating capacity were examined in different experimental conditions, such as isoprenosine, pustulan or spores of strain ATTCC 1999 B subtilis. The therapeutic index of these substances appears to be very high and at least, for one of them, their activity was also observable after oral administration.
In the same research area, the group in Paris (Association Claude Bernard), studied the properties of a two immunomodulatory chemically defined drug azimexon and tuftsin, on the immune response in mice. Likewise, levamisole and bestaline chronic treatments were administrated to aged immunodepressed mice and their effects were observed on tumoral and cellular immune responses. Bestalin as well as levamisole were found to induce a significant reduction of spontaneous tumor incidence and an increase in life span. Levamisole was able to prevent the age-related appearance of suppressor cells. The effect of azimexon administration to immunodepressed cancer patients was also studied by the same group. The compound was found to be non toxic and to possess powerful immunorestorating properties.

The aim of these studies carried out on the development and use of immunostimulatory agents was a better understanding of their mode of action for a safer and more effective use of them. The great number of results obtained during the last programme constitutes a major improvement in this field.

2.3.3. Infection after irradiation

Many factors endanger irradiated patients. The importance of the alterations of their immune system, the number of potential pathogens present and their virulence must be carefully considered before choosing an appropriate treatment. Different points, important for a better knowledge of the biological alterations due to irradiation have been studied during the last programme.

The group at the university of Florence studied radiation damage and repair processes of the small intestine of female Wistar rats irradiated at a dose of 600 and 1200 rad. Morphological and biochemical observations were carried out on animals sacrified from 1 hour to 29 days after irradiation. The results showed a good tolerance of the gut epithelium to fractionated doses that, if administered in a single session would kill 37% of the animals by the gastrointestinal radiation syndrome.

The group of Louvain studied the abnormalities caused by irradiation to the gut mucosa and, particularly, to which extent the impermeability of the gut barrier can be impaired by exposure to ionizing radiation from 5 Gy to 40 Gy. The gut permeability was studied either by oral administration of iodinated human serum albumin and measure of the labelled molecules in the blood stream or by intravenous injection of markers and monitoring in the tissues by electron microscopy. In conclusion, there was no clear rupture of the intestinal epithelium in sublethally irradiated animals and then, no reason to believe that microorganisms can reach the blood stream of irradiated organisms by a direct diffusion mechanism from the gut lumen.

The presence of "natural killer" activity was described in the intestinal mucosa by the "Mario Negri" group in Milan.

Pathogenesis of post-irradiation infections has also been studied by the group of Louvain, using a non pathogenic microorganism, Yersinia enterocolitica intravenously injected into irradiated rats. The results indicated that immunity mediated by T or B lymphocytes is not always

implicated in post-irradiation infections. Factors such as macrophages, granulocytes or eosinophils should also be considered.

These results, altogether can be considered as a great improvement in the basic knowledge of radiation damage to the immune system and its possible treatment.

2.4. Bone marrow transplantation

Bone marrow transplantation can be successfully used, in certain conditions, to treat irradiated patients suffering from the hemopoietic syndrome. Great improvements of the technique have been obtained during the last years, due to the contribution of specialists in haematology, immunology, oncology. However, problems still exist in the clinical use of bone marrow transplantation, principally due either to the rejection of the graft or to the appearance of a graft versus host disease (GVHD).

The group in Munchen concentrated on tissue typing for bone marrow transplantation in supralethally irradiated dogs. They established a "mixed lymphocyte culture test" and used it for the definition of lymphocyte define "mixed lymphocyte culture" determinants. They concluded that DLA-A differences led to failure of bone marrow engraftment more often than differences in DLA-B and DLA-D. The DLA-A locus was also found to contribute to a severe graft versus host disease and therefore, was considered of direct relevance to the treatment of radiation injury in a preclinical animal model. Furthermore, they have obtained a better definition of the T antigen in dogs. Using an immunohistochemical method for the demonstration of T cells on frozen sections of tissues from mice or men, they have been able to develop a convenient T cell test that they have used for the quality control of their rabbit anti-dog thymocyte globulin. Studies concerning the use of these antisera to improve the bone marrow graft treatment are in progress.

The group of TNO, Rijswijk also studied bone marrow transplantation as a treatment for irradiated patients. They used rodents to understand the fundamental aspects of the problem as well as dogs and monkeys in

preclinical experiments necessary to identify the factors that would permit a successful bone marrow transplantation to patients lacking a major histocompatibility complex (MHC) identical sibling donor. Major improvements have been achieved during the past four years by this group. The selection of suitable non related donors in rhesus monkeys is now possible and clinical exploration in patients lacking sibling donors may be started.

The dog model, with its large litters is specially suitable to study bone marrow transplantation in related donor/recipient combinations. It was used in MHC-identical and haploidentical sibling transplantations. The optimal dose of irradiation in different conditions of MHC compatibility and its mode of administration were analyzed, both in function of the takeability of the grafts and also for their late effects on different organs. Results obtained with repeated low dose total body irradiation were encouraging and such experiments will be extended because of their great value for clinical application. The Rhesus monkey, an outbred species like man, was employed to study the possibility to diminish or even to avoid the graft versus host disease (GVDH) after bone marrow transplantation in situations where sibling donor identical for the MHC are not available. Both the selection for histocompatibility and the selective elimination of immunocompetent cells from the graft were studied. The histocompatibility research was carried out on the three classes of MHC products which may play a role. Attention was paid principally to the Ia antigens which were poorly known at the beginning of the present programme. They also identified a new class I (or SD) antigens of Rhesus monkey. They studied the frequency of bone marrow grafts in different donor/recipient combinations using unfractionated bone marrow cells or stem cells enriched grafts, and the percentage of resulting GVHD. In conclusion, the group of TNO (Rijswijk) stresses the importance of matching for class I, serologically defined antigens, in terms of both takeability of stem cell concentrates and mitigation of resulting GVHD. The advantage of a close MHC match with respect to mitigation of GVHD appears to be optimally expressed if the number of lymphocytes present in the graft is decreased. However the use of stem cells concentrates increases the risk of graft failure and clearly indicates the necessity of improving the conditioning.

The group in Ulm, in an attempt to transfer the knowledge obtained from the preclinical dog model, developed a "blood stem cell bank" at the clinical level. A system of closed plastic bag was tested for the collection, cryopreservation, thawing and transfusion of mononuclear blood cells collected from human volunteers. A cellular recovery of 95.7% was obtained, establishing that a "blood stem cell bank" for man is possible. However, further studies are needed before using this technique. According to this group, there is an excellent perspective for obtaining stem cells in man from the peripheral blood in a purified form, by separating progenitor cells from immunocompetent cells, cryopreserving them and restoring patients, probably after an immunosuppressive conditioning regimen.

The majority of research groups in the field of bone marrow transplantation admit that the polymorphism of the genes coding for tissue antigens makes it very unlikely that tissue typing will provide histocompatible donors for the majority of patients. The major objective was then to identify the factors for successful bone marrow transplantation between unrelated patients. Two problems must be solved

a) the so-called host versus graft reaction which results in the rejection of the grafted cells by the host;
b) the graft versus host reaction, which is an immunological attack of the host by the immune cells of the graft. Measures can be taken to avoid the rejection of the grafted cells but they will easily promote the development of a GVH disease. Reciprocally, measures taken to mitigate the GVH disease will increase the number of graft failures. Thus, a successful bone marrow transplantation is still a difficult goal to achieve.

The acute symptoms of GVH disease are known to be due to thymus dependent lymphocytes. Different techniques have been elaborated to decrease or even to eliminate the T lymphocytes and their precursors from the donor cell population namely the discontinuous gradient technology (University of Ulm & TNO, Rijswijk) and the use of polyclonal or monoclonal anti T cell globulin (University of München).

Similarly the group in Rijswijk has demonstrated that the GVH disease can be completely prevented by gastrointestinal decontamination. Different protocols have been tested in mouse, dog, monkey and man. The group in Ulm also studied this technique in mice and humans. Attempts to transfer these results to clinical situations must be pursued.

Major improvements during the 1976-1980 programme have been obtained in basic research as well as in clinical applications. However, the present situation clearly shows that problems of bone marrow grafts are only partially solved. Origin of hematopoietic stem cells, their separation from T lymphocytes, their conservation for a long period of time, the typing of the donor and the host for histocompatibility, the conditioning of the recipients by an immunosuppressive treatment and the prevention of infection and GVH disease by gastrointestinal decontamination are subjects of basic and preclinical research, which have a great impact on clinical applications.

SECTOR D

LONG TERM EFFECTS OF IONIZING RADIATION

Long term effects due to irradiation from external sources or from incorporated radionuclides represent important risk aspects in radioprotection since they can affect a relatively large number of persons and cannot, in general, be prevented once exposure has occured. One should distinguish stochastic late effects- cancer induction and genetic damage -which arise at full severity without a threshold with a certain, although small, probability even at the lowest dose levels, from non-stochastic late effects- vascular changes, fibrosis or atrophy -which develop only above a certain threshold. Stochastic risks are primarily of concern for the protection of the population and, for occupational workers, under normal conditions of operation. Non-stochastic effects would mainly affect persons exposed to large doses accidentally or something following medical treatment.

The Radiation Protection Programme of the European Community has sponsored research on late somatic effects by means of 36 contracts which are most conveniently classified according to the following categories :

1. Purpose and general view

2. Non-stochastic effects.

3. Stochastic effects (induction of cancers).
   - 3.1. by external irradiation.
   - 3.2. by incorporated radionuclides, particularly in lung and bone.

4. Distribution and metabolism of radioelements, particularly that of particles deposited in lung.

5. Decorporation (discharge) of radionuclides from the body.

6. Epidemiological studies on late effects in man.

7. Exposure to radiation from medical diagnostic procedures.

1. PURPOSE AND GENERAL VIEW

One activity supported by the Radiation Protection Programme is the European Late Effect Project Group (EULEP) whose work embraces categories 1-4. Studies on late effects in animals are time-consuming and expensive, and must be carefully standardized with respect to experimental design and animal care. EULEP, an association of about 20 European laboratories aims to achieve such standardisation and performs its tasks by means of two standardisation and three research committees. The committee of dosimetry of EULEP has carried out several intercomparison programmes in member laboratories for dosimetry of whole body and partial body X-ray exposure. As a result, errors in dosimetry in participating laboratories were corrected to bring dosimetric procedures in EULEP laboratories to an acceptable degree of reproducibility. The committee of pathology maintains a Consultation Centre to help member laboratories to establish pathological diagnoses in difficult cases. It also holds regular slide seminars where discussion among different scientists has succeeded in standardizing the terminology of histological diagnosis of late radiation effects, a prerequisite for comparing data from different laboratories. An important product of this undertaking is the publication of an Atlas which is appearing in installments and deals with important subjects of experimental and radiation pathology.

The research projects coordinated by EULEP are related to three areas :
- pathogenesis of radiation induced neoplastic diseases,
- pathogenesis of radiation induced non-neoplastic diseases and
- action of internal emitters.

Support of research by EULEP is essentially catalytic, fostering cooperation between different laboratories. As an example, a project studying the pathogenesis of radiation induced non-stochastic late vascular damage in the rat central nervous system involves 6 research groups from 4 countries and approaches the problem under standardized conditions with respect to morphology, vascular architecture, blood flow, physiology and biochemistry. Other cooperative projects have also secured the participation of scientists from outside the European Community. Specific research projects coordinated by EULEP (number of participating laboraties given in parenthesis) deal among other things with the changes preceding the appearance of radio-induced leukemia (4) in rodents, the role of viruses in the development of leukemia and of bone cancer in mice (2), the induction of lung tumours (3) in mice, the

development of vascular damage in the hamster cheek pouch (2), the role of different factors in the pathogenesis of lung fibrosis (3) in rats, the development of bone and lung cancer in rodents after incorporation of radionuclides (4), the hazards of tritium (4), the late effects after inhalation of radionuclides (4), and the decorporation of radiactive isotopes from contaminated organisms (4). In addition, EULEP organizes yearly meetings on critical topics of late effect research in cooperation with relevant international societies in order to stimulate discussion and understanding of the late effects of radiation. The proceedings of these meetings have been published with the aid of the European Community. Thus, EULEP can be considered as an example of successfully coordinated research on an international scale.

2. NON-STOCHASTIC LATE EFFECTS

Non-stochastic late effects arise only if a certain threshold dose is exceeded. Consequently, they are normally seen only in heavily irradiated organs (equivalent to more than 10 Gy delivered in a short time) as sequelae of intensive radiation therapy or after accidental exposure to industrial and medical radiation sources. Standards of radiological protection are partially based on prevention of non-stochastic effects although the data on which such standards rely are fragmentary for exposure in man. Thus, there is a need to establish dose effect curves and to elucidate the pathophysiological mechanisms of action of non-stochastic effects as well as to explore the possibilities for intervention after exposure, to prevent the development of the deleterious sequelae and for treatment of late symptoms once they have developed.

Non-stochastic late effects are characterized by atrophic and dystrophic lesions that impair organ function to such an extent that they may contribute to other diseases resulting in death, in some instances after long periods. The principal pathological mechanism involved in non-stochastic lesions are :

2.1. damage to blood vessels with deleterious consequences for tissue oxygenation and nutrition,

2.2. abnormal formation of connective tissue (fibrosis) leading to a reduction and replacement of parenchymal tissue,

2.3. atrophy of the functional parenchymal tissue

2.4. in some cases, damage to nervous structures.

In man, late damage in skin and lung are most commonly seen, particularly after radiation therapy, but late lesions in the gastrointestinal tract, bone-marrow, thyroid, eyes, bone and the developing embryo may also occur and have been studied in experimental animals.

Early and late effects in pig skin, which in many respects resembles human skin, were compared (Univ. Oxford) using a wide range of complementary assay techniques. A first wave of reaction due to effects on both, vasculature and epithelium, reaches its peak 4-6 weeks after irradiation with 8-23 Gy and is characterized by erythema and an increase in blood flow and skin temperature. These changes are thought to be related to epithelial cell death. Later, 10-16 weeks after exposure, radiation damage of dermal vessels with decreased blood flow and skin temperature and occulusion of arterioles is prominent, if the dose had been high enough (>20 Gy) dermal necrosis can result. Dose fractionation, as used in radiotherapy, reduces the severity of the alterations in both epithelium and vessels, but more markedly in the vessels, so that severe vascular reaction and necroses are absent or minimized after fractionation.

The hamster cheek pouch allows observations in the living animal so that the development of vascular alterations with changes in vessel wall/vessel volume ratio can be followed over the entire postirradiation period (Univ. Oxford). Two waves of reaction, at 3 and at 9-12 months, were observed after acute doses of 20 Gy or more. After lower doses, the changes were less severe and shorter. The first wave of vascular damage, during which blood flow is reduced and morphological alterations in small arterioles such as localized narrowing of the lumen are found, is thought to represent the primary vascular response.

Lung damage is characterized firstly by an inflammatory response (pneumonitis) and later by fibrosis and can be caused by both external irradiation and inhaled radionuclides. Prior to the accumulation of collagen (CEN Mol) which characterizes fibrosis and which, dependent on the radiation dose, commences at 3 to 9 months after thorax-exposure of rats, blood flow is reduced, lysosomal enzymes are activated, and lipids and fibrinolytic activity are diminished. All these changes may contribute to the pathogenesis of fibrosis. Thus, a decreased capacity to remove fibrinogen due to a reduction of plasminogen activator in the

wall of the blood vessels, could interfere with the resorption of the exudate deposited during the early period after irradiation and thus result in an immigration of fibroblasts, and connective tissue formation in these areas. A decrease in pulmonary lipids may reflect an altered synthesis of surfactant by type II alveolar cells (pneumocytes). Tissue anoxia from a reduced blood flow could damage lung functional parenchyma which then is replaced by fribrotic tissue.

Studies on irradiated rat brain (CEN Mol) deal with biochemical aspects of the mechanism of vascular alterations. Brain was chosen for these studies because changes in cell population, which make interpretation difficult in some organs, is relatively unimportant in the CNS and because brain irradiation has now become a standard technique in leukemia treatment of children. Short time exposure of the brain to 20 Gy or more affected several biochemical parameters as well as blood flow. Serotonin content increased in a way dependent on the dose from 3 to 9 months after irradiation. A dose-dependent increase was also found for hydroxyproline, a constituent of collagen, and for lysosomal enzymes. Sialic acid, which occurs in myelin and in cell membranes, diminished. Cerebral blood flow, measured by means of radioactive microspheres, was depressed early after exposure and increased later. These observations, in the context of those of the other participants of the EULEP study, indicate that changes in nervous functions and collagen deposition develop in parallel with vascular damage.

Thyroid is a critical organ when radioactive iodine isotopes are incorporated or when the neck region is subjected to external irradiation. In order to obtain a model system for the study of the action of radiation, sheep thyroid cells were cultured (Coll. Technology Dublin); they were found to preserve many morphological, functional and radiobiological characteristics of the normal thyroid. These cells are relatively radioresistant (D_o : 4 Gy) and have a low extrapolation number. Their iodine trapping activity was also affected in these cells after gamma ray exposure. Other studies carried out under this contract investigated the influence of thyroid size and shape on measurements of thyroid uptake of different iodine isotopes and of Tc-99m, and followed iodine kinetics in human thyroid by means of thermoluminescent dosimetry.

3. STOCHASTIC EFFECTS (INDUCTION OF TUMOURS)

The objectives of research on radiation carcinogenesis are to establish the dose-effect relationships for cancer induction in animal models, to compare and eventually extrapolate them to the human situation; to define conditions under which ionizing radiation, particularly at low doses, can induce cancers; to characterize the cells and tissues at risk for cancer development; to evaluate the factors (virogenes, oncogenes, hormonal and immunological status etc) which contribute to the development of the cancer.

3.1. Carcinogenesis after external irradiation

Whole body exposure to ionizing radiation can result not only in death from acute effects but also in a reduction in life span. An increased incidence and earlier appearance of different cancers is the principal cause of such precocious death after low doses of radiation (CEN MOL). In addition, renal and pulmonary diseases, as well as fibrosis in various organs, can shorten the life of animals surviving the acute crisis after higher doses (>5 Gy). Radioprotectors, particularly when given in combination to mice, which reduce short-term mortality after acute irradiation are effective against diseases shortening the life span, in particular against thymic lymphoma and to a lesser degree against myeloid leukemia, sarcoma, glomerulosclerosis and non-cancerous lung lesions. A similar protection is also achieved in animals submitted to irradiation fractionated into 4 exposures at weekly intervals.

Two research teams (CEN Mol and Fond. Bergonié Bordeaux) concerted a study into the role of viruses in radiation-induced murine leukemia. The leukemogenic potentials of the B1/F virus complex could be attributed (CEN Mol) to distinct viral entities as shown by the behaviour of clones isolated from this complex. This was also confirmed by molecular hybridization which indicated that the DNA was only partially homologous, as well as by the immunological behaviour which showed that the gp70 constituents of the virus envelope are type specific. It is noteworthy that, although this virus could propagate in rats, it did not contain detectable rat DNA sequences. The possible role of endogenous retro-viruses in radiation-induced leukemia (Fond. Bergonié Bordeaux) was analyzed by cloning a cell line capable of producing the RadLV-Rs virus.

It could thus be demonstrated that the RadLV-Rs as well as the similar 13-3C virus consisted of at least two components, the one B-tropic, the other X-tropic (xenotropic). The endogenous N-tropic virus was only seldom found in leukemic tissue and never induced leukemia. If the B-tropic virus was injected into mice leukemia resulted and the latent period depended on the spontaneous expression of the X-tropic component. Two B-type viruses were defined, one grew well on fibroblasts but did not induce leukemia, the other grew on cells isolated from thymus (TAC) and was leukemogenic.

The human mammary gland is sensitive to radiation carcinogenesis and information has been obtained by animal experiments on the effects of low doses, on the RBE of neutrons and on the promoting effects of hormones.

Investigation (TNO Rijswijk) in several rat strains indicated that with increasing dose the incidence of mammary tumours increased, and the latency period was shortened. There were differences in susceptibility and spontaneous incidence between the strains studied. At a 30% prevalence level, a RBE between 8-20 was found for 0.5 MeV neutrons and a RBE between 2-4 was found for 15 MeV neutrons, values which are lower than those observed at low dose in another strain by others. Following fractionated exposure, repair with respect to carcinogenesis was observed after neutron as well as after X-ray irradiation, and the RBE for fractionated neutron irradiation was in the order of 10.

Many cancers arise in old age, and it appears of interest to see whether cancer induction by irradiation also follows a similar course. External beta or ultraviolet irradiation induced cancers more readily in senescent than in young mouse skin (Univ. Copenhagen) even when skin from old animals had been grafted to young animals. Such old skin had a lower content of extractable mitotic inhibitor and, in addition, had a lowered response to this inhibitor and thus could control the rate of normal cell division less well. Beta-irradiation which may disturb cell division and its regulation caused an increase in content of mitotic inhibitor 3 months later.

3.2. Carcinogenesis from internal irradiation due to incorporated radionuclides

The malignant tumours observed in man after internal irradiation include bone sarcomas and leukemias after incorporation of bone seeking radium radioisotopes, liver cancers after injection of thorium and thyroid cancers after exposure to radioiodine. A wider spectrum of malignant tumours has been demonstrated in animals and may thus potentially also arise in man. These include bone cancer and leukemia after injection of actinides and alkaline earths, and lung and liver cancer after exposure to both alpha and beta-gamma emitting isotopes.

3.2.1. Bone tumour induction

The evaluation of the risk to man from bone-seeking radionuclides, in particular from actinides, requires information originating both from animal experiments and from epidemiological experience from human exposure to radium isotopes, taking into account the spatial and temporary differences in the exposure of bone cells.
The induction of osteosarcomas in mice by different radionuclides was studied as a function of dose and of its temporal and spatial distribution (GSF Neuherberg). Repeated administration of ^{224}Ra, giving an absorbed dose of 11 Gy over 36 weeks, increased the osteosarcomas frequency and shortened the latent period compared to single administration of the same amount of ^{224}Ra. A similar protraction effect has also been demonstrated in experiments with repeated application of the short-lived beta-emitter lutetium-177. When the short-lived alpha emitter thorium-227 was given together with a small amount of its long-lived mother nuclide actinium-227, the effect on osteosarcoma induction exceeded that expected from an additive behaviour. In consequence of these observations, one may expect that short-lived radionuclides, particularly in multiple administrations, may be more hazardous than a single administration of a long-lived radionuclide. It is also noteworthy that the risk of radiation induced osteosarcomas was the same in young and in adult animals, and in strains with low and high spontaneous osteoma incidence. Several factors influencing bone metabolism were tested with respect to their ability to promote osteosarcoma formation. Fluoride had no influence on osteosarcoma

induction by ^{227}Th; beta aminopropionitrile, a substance which interferes with collagen deposition, reduced the latent period but did not affect the incidence of osteosarcoma. The osteosarcomas induced by administration of ^{224}Ra and ^{227}Th to C3Hx101 hybrid mice were associated with the expression of C type retro-virus particles which were detected by electron microscopy and by several tests, for example ELISA, gradient centrifugation and in vitro cultivation of the cancer cells. Viral p30 protein could be found also in spleen, kidney and serum of osteosarcomas bearing mice. Virus appeared as early as one month after exposure began; subsequently, antibodies directed against the gp70 glycoprotein of the viral envelope increased markedly. At the time of osteosarcomas appearance, viral antibodies diminished, retrovirus was expressed in bone tissues, and viral p30 proteins appeared in serum.

Osteosarcoma incidence after injection of monomeric plutonium-239 to mice was studied (CNEN Casaccia) in order to obtain better information on the shape of the dose effect curve in the low dose range. Retention functions for plutonium were determined for bone, liver, kidney and total body. The mean skeletal doses until the end of life expectancy ranged from 0.006 to 0.6 Gy. About 2000 animals have been injected and are being followed for the incidence of osteosarcomas. The retention data agree with those published by others, but show, in addition, a component of low turnover in liver. The microdistribution of plutonium in bone is being studied in cooperation with the KFZ Karlsruhe and MRC Harwell.

The microdistribution and retention of plutonium-239 in skeleton and other tissues of the female mouse were studied (MRC Harwell) in order to create a basis for dosimetric assessment and to correlate dose with the development of cancers. Neutron-induced autoradiography and alpha-radiography were utilized in semi-automated techniques to assess the spatial distribution of plutonium on the periosteal and endosteal surface of selected bones (ilium, femur, 3rd lumbar vertebra and central caudal vertebra) at different times after administration. At 24 hours after injection, plutonium was concentrated at the bone surfaces, the concentrations being about four times greater at endosteal than at periosteal surfaces. Subsequently, plutonium became increasingly buried in the cortex of the ilium, and the endosteal peak concentration disappeared; however plutonium remained associated with periosteal surfaces. At 6 and 12 months after injection, plutonium had become

randomly distributed through the bone, and in this respect, behaved similarly to radium-226. Differences in distribution occurred at the various dose levels, particularly with respect to the dose to the bone marrow.

Invasive growth appeared to be related to the proteolytic ability of the cancer cell as well as to other factors. Plasminogen activating enzymes could participate in such local tissue destruction, and inactivation of this enzyme may interfere with the expansion of the tumour. Malignant murine tumours, including those induced in bone by treatment with strontium-90, contain a plasminogen activating enzyme with a molecular weight of 48 000 Dalton (Univ. Copenhagen). This enzyme was purified and characterized. Antibodies against the enzyme were prepared with a high degree of specificity and found to inhibit the enzyme in vivo for several days. Such antibodies may help to clarify the role of plasminogen activator in induction and invasive growth of cancers induced by irradiation.

3.2.2. Lung tumour induction

Radioactive particles which are retained in lungs of animals for short or long periods can cause cancer. The principal objective of the research on lung cancer after radionuclide inhalation was to determine the relation between the distribution of the dose from such particles and the cells at risk (the "hot particle" problem).

Fission fragments can produce localized high doses in lung, and so it is possible to study the effects of inhomogeneous distribution of dose. Rats inhaled $^{235}U_2$ particles (2.5-2.8 μm diameter, 40-400 μg) which were irradiated in situ with thermal neutrons (MRC Harwell) 20 hours or 7 days later to induce fission. Control groups included animals treated only with neutrons and animals which were exposed to neutrons before the inhalation. More malignant lung tumours were observed in the animals exposed to neutrons after inhalation of the particles than in the non-irradiated ones, whereas exposure to neutrons before inhalation had no such effect. Thus, lung cancer appeared to be induced mainly by the alpha rays, giving a dose of 6 Gy during 600 days, from the uranium-235 and not by the neutrons, but fission fragments may contribute to lung cancer induction. The $^{235}UO_2$ particles were rapidly phagocytosed by

macrophages to form aggregates or foci. The number of such foci, as studied by neutron induced autoradiography, was proportional to the number of macrophages in lung up to a particle content in lung of 0.2 mg. At higher doses than 6 Gy from $^{235}UO_2$, the number of such aggregates increased.

When mice inhaled small or large sized (0.8 or 2.2 μm diameter) $^{239}PuO_2$ particles at activities from 3.7 to 926 Bq (St. Bartholomew Hospital London), the percentage of mice with lung tumours increased significantly after one year. Adenomas and adenocarcinomas occurred in about equal numbers and originated mainly from the alveolar region and rarely from bronchi. The incidence of lung tumours was highest at an activity of about 111 Bq and decreased at higher activities owing to the shortened survival times caused by radiation induced pulmonary insufficiency. The histopathology of lungs exposed to high activities (of 740 Bq or more) was characterized by the accumulation of abnormal giant macrophages, some of which filled the alveolar spaces and were often associated with areas of fibrosis and alveolar cell hyperplasia. The number of animals which have died to date is still insufficient to assess the effect of particle size on long term survival.

4. DISTRIBUTION AND METABOLISM OF RADIONUCLIDES, PARTICULARLY OF PARTICLES DEPOSITED IN THE LUNG

Inhalation is an important route of entry for contamination by radioactive particles. An understanding of the mechanisms of deposition and clearance of such particles in lung is necessary in order to predict the consequences of human exposure. The ICRP have recommended a model for the behaviour of particles in lung, and the studies in this category represent an attempt to examine the general applicability of the model in radiological protection and the potential range of its parameters in a human population. The studies confirm that the model is valid in general terms but deviations have been observed with certain types of particles. Moreover, it may be preferable to use individual rather than general parameters for dose calculations. These conclusions are based on investigations in animals as well as in humans. The latter involved accidentally exposed workers and volunteers breathing inert particles.

4.1. Human studies

Human volunteers (NRPB Harwell) inhaled tagged aluminosilicate glass microspheres (1.2 um or 3.9 um diameter) Approximately 8% of the small, and 40% of the large, particles were cleared within 6 days. No rapid (1 day) clearance phase, as assumed in the ICRP model, could be detected. About 3% of the small and 15% of the large particles had a clearance half time of 20 days, and the rest had half times between 320 and 520 days, but with large intersubject variability. The latter half time corresponds to the slow phase of clearance of insoluble particles defined in the ICRP model. Half times for the dissolution by lung macrophages were estimated at 700 and 1400 days for small and large particles respectively. In addition, the clearance of such inert tagged aluminosilicate particles in rats was compared with that of plutonium oxide particles which could cause damage to lung. On the basis of relative clearance of both types of particles, one may predict the behaviour of plutonium oxide particles in human lung.

Observations on clearance of plutonium from lungs and urinary excretion after accidental plutonium oxide inhalation in man (AERE Harwell) do not agree entirely with present models. Following intake, about two thirds of the material deposited in the respiratory system was excreted more rapidly than predicted by the model. After this early clearance phase, two clearance components with half lifes of 30 and 300 days could be identified, and a small component, perhaps associated with material retained in lymph nodes, was also observed. Changing the parameters of the ICRP model to take into account a possible intermediate component would yield a better fit than that predicted by the ICRP modell which has no intermediate component, although this would imply major changes in dose assessments. Mathematical compartment models were developed to select the best formulation for dosimetry of the individual or group. Thus, it would appear more appropriate to consider intakes of radiochemicals on an individual basis if the physical and chemical properties of the inhaled material were known, rather than applying a generalised model. On prerequisite for such a modelling would be a reliable method of measuring the plutonium lung burden in man. The thickness of the chest wall greatly affects plutonium measurements as a result of the marked tissue absorption of the X-ray emitted by ^{239}Pu, and this thickness was measured by ultrasound.

Deposition and short term clearance were studied in human volunteers using polystyrene particles (2.5, 5 and 7.5 μm diameter) labelled with ^{99m}Tc (AERE Harwell). Total deposition and its dependence on particle size were in good agreement with the revised ICRP model. Differences in regional deposition are more difficult to assess but the agreement with the model was still satisfactory. Some deviation from the predicted values was noted with respect to short term clearance since particle size did not influence the length of time during which the rapid clearance was operative but rather affected the rate of clearance. Mucociliary escalator action, rather than phagocytosis by macrophages, seems to be the mechanism by which the short term clearance is mainly effected. This assumption appears to be supported by the observation that smokers have a more rapid early clearance phase than non-smokers, perhaps owing to an enhanced mucociliary clearance. On the other hand, it had been usually thought that smoking impairs the mucociliary action.

Long standing contamination by americium-241 (several months to about 10 years) from inhalation, displayed a biological half life in the body of more than 30 years (AERE Harwell). Movement of activity within the body from lung to bone and liver still took place, however, except in one person where exposure had occurred many years previously. Another person contaminated with both ^{238}Pu and ^{241}Am was followed from 7 days after the accident and exhibited a much greater early clearance for americium than for plutonium. At later times, both nuclides had effective half lifes of more than 500 days.

The physical and chemical characteristics of dusts released in the uranium industry were studied (CEA Pierrelatte) in order to obtain information on the risk of such dusts. The dusts consisted of different uranium oxides, uranates or uranium tetrafluoride and had particle sizes from below 1 to about 40 μm. About 40% of the dust was soluble within 48 hours. Sampling at various places in the working environment indicated that about one quarter of the air samples had uranium contents exceeding the recommended limit so that corrective action had to be taken. Persons who were found to be contaminated with uranium were withdrawn from exposure and showed no elevated uranium urine values after a few weeks.

4.2. Animal studies

Although ultimately only studies on the behaviour of aerosols in man can validate a human model, investigations in animals can help to obtain more detailed information than is possible in man on the mechanisms and kinetics of long term retention and clearance and on macro- and micro-distribution in tissues and thus provide important basic information for modelling.

The inhomogeneity of dose distribution from radioactive particles inhaled in lung has been studied (Polytechn. London). The "specific energy" delivered to elemental volumes of rat lung cells by plutonium particles of different sizes deposited on the alveolar wall was estimated on the basis of image analysis of lung sections. The lung was inflated at a defined pressure, and 50 possible alpha tracks emitted by plutonium particles assumed to be situated at different sites in the lung parenchyma were followed on the digitized image. Histograms of all volumes receiving a specific energy within a certain energy interval were obtained in this way. Assuming a life span of cells of 100 days, volumes which had received a given specific energy during a mean cell life from a maximal permissible lung burden could be calculated. From the data, it appeared that only a relatively small percentage of the cells were hit and less than 1% would be killed if killing were assumed to occur with a single exponential function of a D_o of 1 Gy. Since rat and human lung are structurally similar, differing by a scaling of about 3 with respect to alveolar size, these calculations can be applied to man.

Movement of inhaled actinide oxides from lung to blood is related to the proportion of small particles present (NRPB Harwell). Positively charged PuO_2 particles also have a high affinity for phospholipids in lung surfactant and, as a consequence, are avidly taken up by macrophages. Thus they are not all available for rapid entry in the blood, and some will translocate to the blood only after a delay. In contrast, negatively charged curium dioxide particles do not react with lipids and diffuse passively into the blood. About two-thirds of the activity entering the blood is transported to liver and bone, and the remainder is excreted in urine. Injection of a chelate following inhalation prevents binding to proteins in the blood, and as a consequence most particles entering blood (>90%) are excreted in urine. Actinides reaching blood in

soluble form -as distinguished from particles- predominantly react with serum proteins to be transferred into cells, and a small fraction is excreted in the urine as the citrate complex. These investigations help to explain the different distribution patterns of inhaled actinides and have suggested methods for enhancing their excretion.

Using an excised ventilated pig lung (NRPB Harwell) it was shown that free lead ions were deposited preferentially in the upper airways. However, there is a translocation of a fraction of these free ions to the blood, and in the process the basal cells of the airways are irradiated to a higher degree than the ICRP model predicts.

Insoluble particles ($BaSO_4$, UO_2) deposited on the wall of the distal trachea of the rat are not completely removed by rapid muco-ciliary clearance as suggested by the ICRP model, and about 1% remains in the trachea for at least 30 days (MRC Harwell). The particles retained become buried in the wall and are taken up by macrophages near the basal cells of the epithelium. Image analysis demonstrated that between day 7 and 35 after inhalation of UO_2 particles, 4% of the lung burden was associated with the airways as opposed to 0.01% predicted by the ICRP model. Although particles thus retained in the airways do not represent a very large fraction of the total, they may be significant for inhaled insoluble alpha emitters as they are retained near the sensitive basal cells.

Hamsters exposed to actinide-containing dusts under conditions that occur in the nuclear industry (NRPB Harwell) cleared about one half of the deposited material with a half-time of 20 days; the remainder had a half life of 240 to 1000 days, the longest retention occurring in animals given the highest dose. The severity of lung fibrosis was related to this retention. Comparatively more ^{238}Pu than ^{239}Pu moved from lung to blood, perhaps because of the faster rate of fragmentation to small (1μm) particles as a result of the high specific activity of the Pu-238 particulates. The overall rate of translocation of Pu-238 from lung to blood was, however, less than predicted from in vitro measurements of solubility because some of the plutonium was entrapped in macrophages. Lung clearance of americium oxide associated with plutonium oxide resembled that of plutonium oxide alone, in contrast to the behaviour of pure americium oxide particles. Moreover, a relatively smaller amount

than predicted by the ICRP model of dust containing uranium, plutonium and americium was deposited in lymph nodes, liver and bone of hamsters. These observation underline the fact that actinides inhaled as minor constituents or in combination with other elements may behave differently from pure materials.

The behaviour of $^{239}PuO_2$ particles (0.88, 1.55 or 2.2 μm diameter was also studied in mouse lung (St Bartholomew's Hospital London). Maximum alveolar deposition occurred at a smaller particle diameter in the mouse than in the rat. Retention was affected by the number of particles (hence dose) but apparently not by their size (NRPB Harwell) and was characterized by two clearance components with half lifes 50 and 210 days.

One project (NRPB Hawell) in this category dealt with the doses from incorporated ^{14}C. The metabolism of different carbon-14 compounds was followed in rodents. Effective dose equivalents and annual limits of intake were calculated assuming the applicability of the data to man.

5. DECORPORATION OF RADIONUCLIDES

Radionuclides accidentally taken up into the body through the lungs, gastrointestinal tract or wounds can exert a deleterious influence for long period of times. Decontamination before the radioisotope has entered body tissues, or before it has reached sites of long-term retention (e.g.bone), or remobilised from such sites, may be of help in reducing such risks, particularly in the case of actinides and alkaline earths. Three types of such compounds were studied.

Alginate (CEN Mol), a natural polysaccharide, added to the food or injected intraperitoneally can increase substantially the excretion of radioactive radium, strontium and lead, even if incorporation had occurred several months before. Alginate in the intestinal lumen appears to bind strongly to these radionuclides shifting the bone-blood-intestine equilibrium so that more of these radionuclides are excreted. Once alkaline earths have become buried deeply in the bone structure, they are probably no longer influenced by decorporating agents, but alginate can still attach to radium deposited near the endosteal surface. This is of

value because this radium lies in proximity to sensitive endosteal cells and stem cells in the marrow. Thus, alginate treatment reduced damage to blood stem cells as measured by a colony assay and so might also diminish the induction of osteo-sarcoma.

The structure of cryptant-222 (GSF Neuherberg) was designed so that it should bind specifically to certain alkaline earths. If given in non-toxic doses shortly after administration of radioactive barium, cryptant substantially reduced retention in the body. Higher and potentially toxic doses were needed to produce a similar effect after injection of radioactive strontium and radium. The pharmacokinetics and toxic properties of cryptant-222 were also characterised in this study. An insoluble derivative of cryptant was developed and tested as a decontaminant to prevent reabsorption of non-absorbed or excreted Ba, Sr, Hg, Cd, Tl and Pb from the intestine. Other studies demonstrated that some remobilisation of barium deposited in bone can be achieved by specific dietary regimes.

Most chelating agents such as DPTA are only partially effective in decorporating plutonium because, being hydrophilic, they cannot enter the cell and reach intracellular deposits. A new chelating agent, Puchel, (prepared at NRPB Harwell) was more lipophilic and more effective than DTPA in removing plutonium from hamsters even if injected as late as three days after administration. Puchel could remove plutonium from the liver of hamsters and most of the mobilised activity was excreted in the feces; but it was ineffective in rats and was only marginally effective in removing plutonium from bone in either species. When Puchel was given as an aerosol it could mobilize some soluble plutonium from the lungs. It also increased resorption of plutonium from wounds, but this may be undesirable in practice since the mobilised plutonium is deposited in liver and bone. Agents which diminish blood flow appear more useful as they cause retention of material in situ whence it may be removed surgically. In practical terms, DTPA remains the only useful chelating agent for soluble actinides but little is known about its behaviour in man. Studies in volunteers suggested that it is more useful to give DTPA as an aerosol than by intravenous injection since therapeutically useful levels are maintained for a longer period.

6. EPIDEMIOLOGICAL STUDIES IN HUMAN POPULATIONS

Information on human populations is needed to complement animal investigations to assess the risks of radiation exposure quantitatively. Two large populations were exposed some 20 years ago to thorotrast used as a diagnostic contrast medium, and to ^{224}Ra for medical treatment. These offer a valuable opportunity to evaluate the risk of internal irradiation in man and are being followed in detail.

A total of 751 patients (378 treated with thorotrast and 373 controls) were followed from 1976 to 1980 (DKFZ Heidelberg). Until now 429 thorotrast and 122 control patients have died. Liver tumours (33.3% compared to 0% in controls) and liver cirrhosis (36.4% compared to 6.6% in controls) were markedly increased to an extent corresponding to the thorotrast dose. Forty percent of the liver tumours were cholangio-carcinomas, 35% were hemangioendothelial sarcomas and 25% were hepatocellular carcinomas. The incidence of myeloid leukemia was elevated in the thorotrast group but was not related to the bone marrow dose. Bronchogenic carcinomas (which might have been induced by exhaled thoron) were not increased in the thorotrast patients. Many of the surviving throrotrast patients suffered from diffuse parenchymal diseases and some of primary liver cancer. The only abnormal laboratory finding in persons who were not clinically ill was a reduced bromosulfthalein excretion, indicating impaired liver function.

In the past, humans have been treated by injection of ^{224}Ra for tuberculosis, various bone diseases and ankylosing spondylitis. The incidence of malignant tumours, in particular of osteosarcomas, and the occurence of exostoses, liver and kidney diseases and cataracts, have been followed in 900 patients (682 adults and 218 juveniles) for up to 20 years after treatment (GSF Neuherberg). So far, a total of malignant 54 bone tumours have been observed. Among 1543 patients exposed to radium-224 in the lower dose range (<0.9 Gy average alpha skeletal dose), two rare malignant tumours of the skeleton have been observed. While this is not statistically significant, it does not rule out the possibility that even low doses could increase cancer risk in bone.

Follow up studies of persons treated with ^{125}I for thyrotoxicosis (Coll.

Technology Dublin) confirmed that the incidence of hypothyroidism increased linearily with dose.

7. EXPOSURE TO RADIATION FROM MEDICAL DIAGNOSTIC PROCEDURES

The largest man-made contribution to the exposure of the general public to ionizing radiation originates from diagnostic medical procedures. Stochastic risks could be significantly reduced if these procedures were optimized to deliver the smallest practicable dose which did not jeopardize diagnostic efficiency. Research in this area has as had its objectives :

a) to assess radiation exposure in medical diagnostic procedures,
b) to investigate ways to reduce the dose to the patient,
c) to compare and improve radiological and radionuclide methods.

The mean absorbed energy per person in the German Federal Republic was estimated to correspond approximately to 30 mJ per year (Univ. Erlangen). This value was based on measurements of organ doses for standard and specialized diagnostic procedures, and on the frequency of the different procedures as collected in an inquiry by the German Federal Board of Health. The stochastic risks from diagnostic procedures include induction of cancer and genetic damage. By analogy to the genetically significant dose, a "malignoma significant" dose was, therefore, defined and calculated to be approximately 400 μSv per year for the German population taking into account the different susceptibilities of the various tissues for cancer induction.

A computer programme was developed (GSF Neuherberg) to calculate organ doses from X-ray diagnostic procedures and these were verified by phantom measurements taking into account age and sex differences in organ size. On the basis of these calculations, a hand book is being prepared which quotes dose levels for all relevant X-ray examinations under normal conditions. Radiation spectra of X-ray tubes used for mammography and dental radiography were determined for all likely settings of tube voltage and filtration. Tungsten X-ray tubes appear more appropriate than molybdenum tubes to radiograph big breasts in mammography, and a better dose reduction in dental radiography can be achieved with aluminum than with samarium filters.

The effects of various factors, including voltage, filtration, target angle and intensifying screens, on X-ray spectra and output of diagnostic X-ray apparatus were studied (AERE Harwell in cooperation with the GSF Neuherberg). A theoretical model for such calculations was established, and a catalogue of X-ray spectra and other relevant parameters (attenuation, exposure rates etc.) was published. Among other findings, it could be demonstrated that K-edge filtration had no significant advantage in reducing the dose in mammography.

Techniques whereby the same diagnostic information can be obtained either by radionuclide or by X-ray procedures, were compared with respect to performance achieved and the radiation dose delivered in a cooperative project of the MRC, London and the University of Pisa. The procedures studied included, in particular, the determination of certain lung, heart, brain and kidney functions. The comparison of both approaches is not yet completed, but evidence has already been obtained that in several cases (e.g. in lung edema, blood flow studies of the myocardium and in the identification of physiological disturbances occuring in cerebral diseases) 90°Compton scattering and radionuclide emission tomography provide more specific and more reliable information than conventional diagnostic radiography.

SECTOR E

GENETIC EFFECTS OF IONIZING RADIATIONS

1. PURPOSE AND GENERAL VIEW

Forty laboratories carried out the programme of the Commission in three different areas of research dealing respectively with :

- the biochemistry of sensitivity and repair
- the nature of genetic damage in eukaryotes
- the modification of dose-effect relationships and the prediction of aberration yields in humans.

The profusion of results, which gave rise to more than 900 publications in scientific journals, is such that they cannot be reviewed extensively in a few pages. Thus, only some of the most significant features of the research carried out are presented in this short report.

2. BIOCHEMISTRY OF SENSITIVITY AND REPAIR

The major objectives were to work out in detail the biochemical pathways leading to repair of DNA lesions in microorganisms and to exploit the knowledge and methods developed on such microorganisms for establishing the molecular basis of sensitivity and of repair mechanisms in man. It is from such research that, ultimately, it will be possible to develop a rational approach to the prediction, treatment and prevention of radiation-induced damage.

2.1. Research with microorganisms

Using several new techniques, including gene cloning methods and the isolation of genes *in vitro*, considerable information has been accumulated by the contractants on the sensitivity of the

hereditary material in yeast and bacteria and on the structure, function, regulation and product of different repair genes. Research of this kind, on lower forms of life, is central to the understanding and the control of mechanisms through which lesions are fixed or repaired and one must keep in mind, in this connection, the fact emphasized by a group of contractants (CNRS, Gif-sur-Yvette; Free University of Brussels; CNR, Pavia) that all repair processes known to occur in man have first been identified in microorganisms.

2.1.1. Molecular nature of induced lesions

In bacteria, the mutagenic specificity is reported to be dose-dependent and base-pair substitutions were found to constitute the major type of mutagenesis after γ-irradiation (University of Leiden). In yeast, X-radiation can induce any type of intragenic mutational change, that is to say either base substitution (of the transition and transversion type) or base loss and base gain with almost equal efficiency (University of Milan). A test-system is now being devised (University of Swansea) for assaying the induction of such point mutations during the meiotic cycle of yeast. Studies of this kind, which at present cannot be carried out on mammalian cells, are important because there is a clear need to find out if the genetic risk to which populations are exposed includes discrete hereditary changes (so-called point mutations) transmissible from generation to generation. Obviously, the work carried out on bacteria and yeast for defining the molecular nature of induced mutations should be extended to more complex organisms and, ultimately, to human cells.

A significant breakthrough for the direct observation of radiation effects on the hereditary material has been made at the University of Åarhus where a single eukaryotic gene of Tetrahymena pyriformis has been isolated in vitro in its functional chromatin form. This gene presents an active region which differs in its chromatin structure from that of the inactive region; it can be transcribed faithfully in vitro by the endogenous RNA polymerase on the active region of the gene

and processing of intervening sequences displays a process of transcription termination which can be regulated in vitro. Analyses of radiation effects on this unique test system now render possible the monitoring of different types of radiation damages, the detection of hypersensitive sites and the development of a very precise in vitro assay for the detection of potential mutagens.

2.1.2. The repair of induced genetic lesions

To identify individual differences in radiosensitivity between humans and to promote preventive or curative interventions against the establishment of genetic damages, the basic requirement is to recognize the products of repair genes and to define their functions and regulation. These objectives have been reached, at least in part, by the contractants at the University of Åarhus, the Free University of Brussels, the University of Dublin, the University of Leiden, the University of Rome, the University of Louvain, at the CNRS (Gif-sur-Yvette) and at the Radium Institute (Orsay). Numerous enzymes, involved in the repair processes or the establishment of damage have been characterized, purified and defined for their functions during repair. Specific genetic sites responsible for the regulation and accomplishment of repair processes have been identified and a multiplicity of different repair systems, often known to operate in man, have been characterized in detail.

Representative examples of the quality and importance of the work carried out by the contractants are to be found, among many other domains, in the areas of research focused upon :

- the elucidation of the process through which the irradiated cell controls the excision and replacement of radiation-induced dimers (excision repair)

- the analysis of the function of one of the essential proteins (RecA protein) which is induced by radiation and plays a central role in cellular radioresistance

- error-prone inducible repair and the possible prevention of radiation-induced genetic alterations

- the genetics and biochemistry of mitochondrial DNA repair.

2.1.2.1. Excision repair

Using recombinant DNA technology, it has been possible (State University of Leiden) to construct plasmids which carry any one of the three E. coli genes (uvrA$^+$, uvrB$^+$, uvrC$^+$) responsible for the removal of radiation-induced pyrimidine dimers on the DNA chain. The location and orientation of these genes on the plasmids have been established. The uvrB protein was found to have a MW of about 80.000 and using an uvrB plasmid carrying only the distal part of the gene, the enzymatic properties in the incision reaction was located at the C-terminus of the protein. The uvrC gene product was identified as a 28.000 dalton protein. It is conceivable, now that all three uvr genes have been cloned on multicopy plasmids, that their gene products will soon be purified and available for biochemical studies. It is anticipated that the main questions concerning the regulation and the mechanism of action of the uvrA, uvrB, uvrC complex on irradiated DNA will be clarified in the next four years. Thus, a model should soon become available for the analysis of the enzymology of the far more complex mechanism of excision repair in human cells.

2.1.2.2. Functions of the RecA protein

The RecA protein, keystone of radioresistance, plays a unique role in the cell. The contractants of the CNRS at Gif-sur-Yvette greatly contributed to the elucidation of its basic cellular functions which include genetic recombination, inducible

error-prone repair, and prophage induction. Cellular resistance to DNA damage produced by X-rays, UV light and chemicals is roughly proportional to the cellular concentration of RecA protein and can be increased if the normal level of RecA protein is artificially increased. It has been found (CNRS, Gif-sur-Yvette) that the RecA protein comprises two main domains, the RecA domain which may direct the constitutive functions of the RecA protein (binding to DNA, control of exonuclease V) and the LexB domain, involved in inducible functions (proteolytic action on repressors). The effects of irradiation on the functions of the RecA protein have been measured at Gif-sur-Yvette and used for developing a specific test which is now used by public institutions and pharmaceutical companies for the detection of physical and potential chemical carcinogens.

2.1.2.3. Prevention of radiation-induced genetic alterations

The demonstrated inducibility of radiation mutagenesis in bacteria and the possibility that mutagenesis and chromosomal aberrations may also be caused by inducible processes in mammalian cells suggest that radiation-induced genetic alterations may be preventable. This possibility suggested by the contractants at the Free University of Brussels is supported by their finding that the protease inhibitor, antipain, inhibits UV mutagenesis in E. coli, chromosomal aberrations in hamster cells, in vitro transformation of mouse cells and in vivo carcinogenesis on mouse skin.

2.1.2.4. The repair of damage to mitochondrial DNA

A group of contractants (Radium Institute of Orsay, University of Louvain, University of Swansea, University of Milan, University of Giessen, University of Göttingen) has taken advantage of the properties of yeast for adapting the techniques and methods used with simple prokaryotes to the far more complex requirements of research on mammalian and human cells. This group has contributed to many different parts of the programme and has unravelled, as far as repair is concerned, the main

pathways to repair and the genetic factors which control them. The importance of the very large collection of radiation sensitive mutants now available in yeast is greatly increased by the possibility, presently explored by contractants at the Radium Institute and in Rotterdam, of fusing yeast protoplasts with repair deficient human cells so as to study the complementation for repair functions. If interaction of human and yeast genomes occurs, the collection of rad repair deficient mutants in yeast will be used to recognize corresponding repair deficiencies in different strains of human cells.

At present, however, it seems that the most original contribution made by the contractants working in the yeast group is the characterization of radiation damage (uv, -rays, X-rays) to mitochondrial DNA and the identification of a variety of the processes through which the different kinds of damage are repaired. Such information, unfortunately not available for human mitochondria, is important in view of the essential functions of mitochondria in the metabolism of the cell. At the Radium Institute, it was found that one type of repair of mitochondrial DNA UV-induced lesions in yeast occurs by photoreactivation and is under the control of one nuclear gene. In contrast, the 10 nuclear genes which govern repair by excision in the nuclear DNA do not act on damaged mitochondrial DNA and yet require mitochondrial integrity for their proper functioning. At the University of Louvain, the bioenergetics of dark repair of UV damage to yeast mitochondrial DNA were explored in details and interpreted coherently. It was also shown that at least 14 genes are involved in the repair of lesions in mitochondrial DNA. At least seven of these are also involved in the repair of γ-rays induced damage of nuclear DNA.

2.2. Research with mammalian cells

The data accumulated in the past by microbiologists and the adaptation of the methods developed on bacteria and yeast for establishing the biochemistry of sensitivity and repair permitted a detailed appraisal of the nature and fate of

radiation-induced lesions in mammalian cells. It has thus been possible, in parallel to a progressive accumulation of knowledge on the enzymology and molecular genetics of sensitivity and repair in man, to establish a basis for direct applications of molecular biology to radiation protection.

The contractants of the Commission (University of Åarhus, MRC at the University of Sussex, College of Technology in Dublin, University of Leiden, University of Brussels, University of Rotterdam, TNO at Rijswijk, CNR at Pavia) participated actively in this research effort and, among many other achievements, contributed significantly to :

- the determination of the properties of polypeptides and enzymes involved in the repair and/or replication of human cells

- the characterization of human cell lines deficient for certain repair capacities

- the appraisal of individual differences in radiosensitivity

- the development of procedures for the prenatal diagnosis of repair deficiencies.

2.2.1. Polypeptides and enzymes involved in cellular responses to radiation

Several enzymes previously described in bacterial systems have been purified from animal cells and characterized. At the CNR laboratory in Pavia, direct involvement of DNA polymerase β in repair was demonstrated for the first time. DNA polymerase γ was shown to be localized in the mitochondria and to be responsible for the replicative synthesis of mitochondrial DNA. DNA-dependent ATPase purified from human cells enhances the activity of α-polymerase and this effect is synergistic with the stimulation caused by the presence of a DNA binding protein purified from calf thymus. A repair assay particularly promising for the detection of effects caused by DNA damaging agents in

human cells was developed. This assay involves the utilization of aphidicolin, a specific inhibitor of the replicative DNA polymerase α, which renders possible the measurement of radiation-induced repair synthesis in conditions relatively unaffected by replicative processes.

In complementation to those findings, the Biology Group of DG XII at Ispra assayed DNA polymerases α and β for their activities with X-irradiated DNA templates. These enzymes were found to recognize mildly irradiated DNA as functional templates, provided that 3'-OH initiating sites pre-exist or are made available by repair nucleases. The same group purified and assayed calf thymus DNA ligase (found to restore physical continuity of the double helical macromolecule with single strand breaks). These findings gave ground to the assumption that mammalian cells like bacteria possess a proof-reading enzymatic system (exonuclease able to perform an editing function during DNA synthesis in vitro) for faithful replication of DNA. The group at ISPRA defined the properties of a DNA glycosylase from calf thymus which removes the uracil occasionally formed or incorporated in DNA and standardized a method for determining the terminal deoxynucleotidyl transferase, TdT, in human malignant lymphomas. Antibodies against TdT were obtained, purified 300-fold and used to standardize immunofluorescence tests for detection of TdT-positive cells by microscopic analysis.

At the University of Åarhus, analysis of polypeptide patterns in prelabelled HeLa cells exposed to lethal doses of X-rays failed to reveal cross-linking to DNA of any of the 150 major nuclear and cytoarchitectural polypeptides involved in the study. A nuclear and a cytoplasmic polypeptide were found to be present in different concentrations in proliferating and in non-dividing irradiated cells; these polypeptides may perhaps be used as useful markers for determining radiation damage at the level of gene expression.

An other approach for assessing the fate of radiation induced damage in cultured mammalian cells involved the preparation of antibodies against pyrimidine dimers and the study, by radioautography, of their elimination by photoreactivation and enzymatic mechanisms. This method, tested successfully at the University of Brussels, still needs to be improved in the case of damage induced by ionizing radiations.

Evidently, considerably more work is needed before a clear picture can be made available of the cascade of biochemical reactions which occur in exposed tissues and of the molecular mechanisms through which pre-mutational and pre-carcinogenic lesions are induced, established or eliminated in human cells. Yet, it is only through such an extension of efforts that it will become possible to understand, predict and prevent the accumulation of deleterious radiation-induced lesions in the human genome.

2.2.2. Inducible and error-prone repair in mammalian cells

Using irradiated SV40 virus, and the single stranded parvoviruses as probes, it was found (University of Leiden, University of Brussels) that survival in monkey and human cells was higher in cells exposed to low UV doses. Similar results were obtained using SV40 DNA as a probe, localizing the reactivation to the viral DNA. A temporal increase in the mutation frequency of SV40 in UV-irradiated monkey cells, and probably also in human cells, is due to the presence of a transcient mutagenic activity in the cells. This together with the kinetics of the survival process now analysed in human cells and monkey cells are indicative of an inducible error-prone repair mechanism comparable to the "SOS-repair" in E. coli.

2.2.3. Repair deficiencies in man

The scope and consequences of such research activities extend far beyond the analyses per se of genetic diseases affecting the repair capacities of man because it is essentially through the study of the misfunction that one can assess the normal function.

2.2.3.1. Genetic studies by complementation analysis

In addition to the five already known complementation groups in excision repair deficient Xeroderma pigmentosum a new complementation group (G) was identified at Erasmus University in Rotterdam through cell fusion. Additional new cell lines from XP patients were assigned to complementation groups and the kinetics of complementation in heterokaryons after fusion of XP cells from different complementation groups were investigated. In postreplication repair deficient cells a procedure was worked out to measure postreplication repair after UV irradiation of fused cells. XP variant cell lines were found to comprise a single genetic complementation group different from group A, C and D. The development of a procedure for complementation analysis of ataxia-telangiectasia (AT)* cell strains revealed the occurrence of different complementation groups within this syndrome which may thus be as heterogeneous, genetically, as XP.

2.2.3.2. Localization of human repair genes

Several techniques were developed at Erasmus University for the localization of genes involved in DNA repair. The general aim of the research was to elaborate a method through cell fusion or

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* Ataxia-telangiectasia has been established by the CEC contractants of the MRC at the University of Sussex (among others) as the first human mutation known to confer cellular radiosensitivity to ionizing radiations.

through the transfer of specific genetic information (chromosomes, parts of chromosomes, DNA fragments) to restore the repair capacity of an otherwise sensitive cell. Promising results were obtained in several instances (transfer of isolated DNA into mammalian acceptor cells, use of a 50% difference in unscheduled DNA synthesis level between human and Chinese hamster cells as a repair marker in human-rodent hybrid cells, use of the fast complementation rate of XP cells belonging to the A group as a marker in cybrids obtained after fusion of XP A group cells with cytoplasts of human-Chinese hamster hybrid cells).

2.2.3.3. Biochemical characterization of repair deficiencies

A considerable amount of work was carried out in this area by the integrated group of contractants at the University of Sussex, Erasmus University, Rotterdam, TNO, Rijswijk, CNR, Pavia, and at the University of Leiden. The complexity and the depths of the analyses performed are such that they cannot be reviewed here in detail. They involved, the development and use of specific methods for the detection of lesions, the measurement of DAN synthesis and the identification of gene products. A very large number of mammalian and human cell lines suspected to be defective in DNA repair were analysed using these methods. Different XP cell lines and XP variant cell lines have been characterized for their levels of dimer removal, their rate of unscheduled DNA synthesis or their capacity to reactivate UV-irradiated SV40 and for the activities of the three DNA polymerases. All the results obtained confirm the important genetic polymorphism detected for the YP syndrome by means of complementation analyses. Additional deficiencies, such as those affecting post-replication repair, have also been searched for and, in certain cases, detected.

Similar approaches were followed for defining several other types of repair deficiencies in man. In ataxia-telangiectasia, for which evidence obtained through a comparison of radiation

effects in G_1 and G_2 stages or by means of various sedimentation and elution methods indicates that the repair of X-ray induced DNA strand breaks may be defective, there is no correlation between hypersensitivity and hypermutability. This finding has led the contractants of the MRC at the University of Sussex to suggest the possibility that in human cells a substantial component of resistance to ionizing radiation is attributable to a repair process which concomitantly produces mutations.

In Cockayne syndrome cells (Cockayne is a UV sensitive syndrome) DNA replication was found to follow abnormal kinetics.

2.2.4. Individual differences in the radiosensitivity of man

One of the main conclusions from the integrated research effort of the group of contractants working at the University of Sussex, Erasmus University, Rotterdam, and the University of Leiden through their analysis of cellular sensitivity for ionizing radiation in a variety of cell strains is that there is considerable variation in radiation sensitivity in human cells. At the University of Sussex the overall range in observed D_o values was 38-180 rads with a lower limit represented by a set of 10 ataxia-telangiectasia cell strains (mean D_o 57 ± 15 rads as compared to 127 ± 17 rads for assumed normal cells). Intermediate sensitivity has been observed in cells from familial retinoblastoma patients, certain Huntington's disease patients, and one XP patient. The contractants at the CNR laboratory of Pavia established that the capacity to repair UV induced DNA damage was lower in cells from seven different cases of Fanconi's anemia and a significant reduction was observed in a cell line heterozygous for the same disease. At Leiden, cells from a patient diagnosed as Blackfan Diamond (pure red cell aplasia) expressed spontaneous and X-ray induced frequencies of chromosomal aberrations which were several times higher than those of the control.

Variations in radiation sensitivity are also to be found within "normal" populations for which the contractants at Sussex University report D_o values for cultured fibroblasts which

extend from 97 to 180 rads. The findings of a wide range of radiation sensitivity in humans are important. They indicate that radiation norms should not be established at the level of populations but at that of the individual and they suggest, in this respect, the possibility of screening potential radiation workers for hypersensitivity to ionizing radiation. There is furthermore evidence that individuals known to be heterozygous for the syndrome ataxia-telangiectasia may have a higher risk of death from all types of malignancy than "normal" individuals.

2.2.5. Prenatal diagnosis of repair deficiencies and other clinical implications

Another important application originating from contractual research on the biochemistry and genetics of repair is the prenatal diagnosis of repair deficiencies. Measurement of post-replication repair in 24 XP cell strains at Erasmus University showed that UDS (unscheduled DNA synthesis) and post-replication repair could also be measured in human amniotic fluid cells. Using such tests it has been possible to carry out prenatal diagnosis on three fetuses at risk of XP.

As knowledge grows of the biochemical deficiencies it should be possible to extend the range of conditions for which prenatal diagnosis is possible. At the same time it should also become possible to improve accuracy and reliability of clinical tests for the detection of repair deficiencies in man. One example among many others of this type of application stems from the research on the rate of semiconservative DNA replication in ataxia-telangiectasia cell strains which showed that DNA synthesis measurement on lymphocytes can be used as a clinical test to support the diagnosis of AT (Erasmus University).

3. NATURE OF GENETIC DAMAGE IN EUKARYOTES

Spontaneously occurring mutations and chromosomal abnormalities are the cause of hereditary defects and disease in man. Radiation can induce mutations and chromosomal abnormalities and the main aim of this work has been to provide the basic information on the occurrence of natural hereditary disorders, the mechanisms of radiation induced effects and the factors which alter the incidence of the induced effects. In this way the assessment of the genetic damage induced by radiation in man, using either the direct estimation method or the doubling dose method, can be developed from a complete understanding of the many processes which are involved.

3.1. Human Meiosis

A technique has been developed (Carlsberg Lab.) which permits a three dimensional reconstruction of meiotic nuclei from primary spermatocytes using serial sectioning and electrol micrography. Using this technique it has been possible to analyse chromosome pairing and chiasma formation and to count the number of recombination nodules and incipient chiasmata. It has been shown that bivalent interlocking is resolved by breakage and a precise reunion of the broken ends; this breakage-reunion process has been shown to be a naturally-occurring phenomenon during chromosome pairing in Bombyx. Meiotic recombination can be associated with recombination nodules and in human spermatocytes these nodules can be observed from the early zygotene stage. The technique allows an analysis of the number and distribution of meiotic recombinational events and also allows a prediction of the level of non-disjunction in human spermatocytes. Biopsies from patients with testis cancer have been obtained prior to treatment with radiation and chemotherapeutic agents; new biopsies will be obtained after treatment and the analysis and comparison of this material will provide information on the long-term effects of radiation on gonads.

In a study of the human ovary (Finsen Lab.) the development of the ovary has been followed in material collected from autopsies and operations. In this way it has been possible to study the normal development of the ovary, early follicle formation starts in the foetus and the progressive stages of follicle development and atresia during infancy up to the first ovulation have been defined. These data provide a basis for a study of the effects of radiation on the ovary and it has been found that the infant ovary is particularly sensitive to radiation which inhibits follicle growth and reduces the number of small follicles. In cases treated by radiation for Wilms' tumour it has been found that the menarche commenced at the expected age but not information is yet available on the fertility of these cases. A study of abnormal ovaries has shown that in some cases, for instance in the case of Down's syndrome, the growth pattern and differentiation of the ovary is disturbed in a way not dissimilar to that caused by radiation.

In a study of the association between impaired gametogenesis and chromosome aberrations (Univ. of Pavia) in human males, a structural chromosomal abnormality has been found in 9% of the cases examined. 7.4% of these abnormalities involved the sex chromosomes. In this special population of males referred from infertility clinics, the frequency of balanced Robertsonian translocations was found to be 10 times higher than that of the general population.

3.2. Non-disjunction in mammals

In an analysis of chromosomes from oocytes at the first meiotic division immediately after ovulation in three different mammals, the mouse, Chinese hamster and Djungarian hamster, different results have been obtained after radiation (Univ. of Göttingen). After treatment of the mouse with doses between 5 and 80 rad no effect of radiation on the incidence of non-disjunction was found. In Chinese hamster, females of different ages were treated with 20 rad. Although no increase in non-disjunction was seen in the age range up to 48 weeks, there was a significant increase in the age group older than 56 weeks. The control in

this experiment was a 8 - 20 weeks old so that it is not completely clear how much of the effect can be ascribed to the 20 rad dose. In the Djungarian hamster, hormonal stimulation can increase the "spontaneous" level of non-disjunction. Using this mammal it was found that 20 rad reduced the level of non-disjunction induced by a hormone treatment even though it increased the number of chromosome abnormalities. These interesting results are interpreted to indicate that radiation can interfere with chromosome segregation during meiosis but whether it increases or decreases non-disjunction seems to depend on the constitution of the treated population.

This interpretation might also provide an explanation for the results of the experiments with the field vole Microtus oeconomus (Univ. of Leiden). In the first series of experiments it has been shown that radiation doses from 25 - 200 rad increased the frequency of non-disjunction although the results indicated some inhomogeneity in the treated population. In a later larger experiment using the same doses no induction of non-disjunction above the control level was found. It was suspected that the differences between the two populations, the first being primarily animals caught in the wild, the second being predominantly in-bred, might explain the different results. In a recent experiment with a different population of voles again no induction of non-disjunction was indicated.

A study of the effects of radiation on satellite association of human chromosomes (Univ. of Galway) concluded that there was no effect on satellite association and consequently the possibility that radiation induced satellite association might increase the risk of chromosome non-disjunction could be discounted.

The effect of radiation on non-disjunction in mammals remains difficult to assess.

3.3. Chromosomal aberrations in somatic and germ cells

One potential method for the assessment of the genetic risk of radiation in man proposes a parallel extrapolation of the

effects induced in the germ cells of an animal via the effects induced in the somatic cells, e.g. blood lymphocytes, of the animal via the effects induced in the somatic cells of man to the effects induced in the germ cells of man. This method has been extensively investigated (Univ. of Leiden) using various stocks of mice, the rhesus monkey, the marmoset and man. In general, dicentric aberrations were scored in blood lymphocytes at the first mitosis following stimulation and, in the testis, reciprocal translocations induced in spermatogonia were scored. In one experiment with mice, reciprocal translocations were scored both in somatic and germ cells. The results of this experiment indicated that the somatic cells react qualitatively in a manner similar to mitotically dividing premeiotic germ cells when the same type of aberration is scored. The sensitivity to dicentric induction in blood lymphocytes was found to be similar for the different mouse variants but one variant had a lower sensitivity to the induction of reciprocal translocations (in the testis) than the rest indicating that the sensitivity of blood lymphocytes to dicentric induction may not parallel the sensitivity of spermatogonia for translocation induction. This impression was supported by a comparison of the ratios of dicentrics in blood to translocations in spermatogonia for the mouse and the rhesus monkey at three doses, the ratio for the mouse was 4, that for the rhesus monkey 10. These results led to the important conclusion that "only direct observations on induced chromosomal aberrations in germ cells of higher primates and man can play a decisive role in estimating human genetic radiation risks arising from chromosomal aberrations".

One difficulty in using the dicentric induction in blood as a measure of the sensitivity of spermatogonia for the induction of reciprocal translocations is that the dicentric is an asymmetrical exchange aberration whereas the reciprocal translocation is a symmetrical exchange aberration and that one makes the implicit assumption that the ratio between the symmetrical and asymmetrical exchanges is constant. Studies have been made to investigate if this ratio does indeed remain constant (Univ. of Leiden, Univ. of Rome) using Chinese Hamster

cells irradiated in vivo and in vitro. The results indicated that there was no change in the ratio in different phases of the cell cycle and in different cells irradiated either in vivo or in vitro.

An additional problem which has been encountered in the studies of aberrations induced in peripheral blood lymphocytes of man (Univ. of Leiden) is that the aberration yield is considerably influenced by donor-to-donor variations and such variations are also found with blood samples obtained from the same donor at different times. A comparison of the sensitivity of man and mouse for dicentric induction revealed an equal sensitivity and the results of this experiment refuted the "arm number hypothesis". A study of the factors influencing chromosome aberrations in mammals (CEN, Mol) revealed however that differences between species in the radiation sensitivity of lymphocytes are greatly attenuated if observations are restricted to the first mitosis. If confirmed for other species, this finding could indicate that the extrapolation of experimental results from animal lymphocytes to human lymphocytes is a reliable procedure.

In a study of the induction of chromosomal abnormalities in oocytes of three different mammals (Univ. of Göttingen) it was found that the sensitivity was dependent upon the stage of oogenesis, the age of the female, and the species examined. These results emphasize the problems associated with genetic risk estimation and with the extrapolation from animal data to man.

An electron micrograph study of a chromosomal aberration which appeared in the light microscope to be a non-reciprocal translocation revealed that a 200 nm piece of the second chromosome was in fact translocated to the end of the first and that the exchange was indeed a reciprocal translocation (Carlsberg Lab.).

3.4. The Doubling Dose Method

The "Doubling Dose Method" is one of the methods currently used to estimate the genetic risk to man; the doubling dose is the dose of radiation which is required to double the spontaneous occurring frequency of genetic defects. Implicit in the use of the doubling dose method is the assumption that proportionality exists between the spontaneous and induced rates of genetic defects and it has therefore been essential to obtain information on the relationships between spontaneous mutation rates and radiation induced mutation rates.

Drosophila melanogaster is a very suitable test object for such an investigation and the induction of mutations at 14 X-chromosome loci has been studied (Univ. of Leiden). The frequency of mutations found at the different loci were compared with the spontaneous frequencies at the same loci and it was found, in general, that there was a good parallelism between the loci having higher spontaneous and induced mutation rates and those having lower spontaneous and induced mutation rates. This result lends some support to the assumption of proportionality between spontaneous and induced mutation rates. Using these results a doubling dose of 100 R per locus can be estimated for specific locus mutations in Drosophila spermatozoa.

In a second study, (null-enzyme mutations in Drosophila, Alcohol dehydrogenase locus, Univ. of Leiden) the spontaneous mutation rate was estimated by screening 400.000 progeny and the induced mutation rate was estimated by screening 300.000 progeny of X-rayed spermatozoa. The total induction rate for null-enzyme mutations was very similar to that for the visible mutations and in addition it was found that about half of these mutations were "gene" mutations and about half were associated with deletions. This latter result was also in accordance with that found for visible mutations. The doubling dose estimated for the "gene" mutations at the alcohol dehydrogenase locus was 73 R which compares very favourably with the 100 R doubling dose estimated for the visible mutations. Of the presumed Adh gene mutations

recovered in these experiments some where shown to produce a non-functional protein and consequently represent radiation induced intragenic changes.

These results taken together provide support for the basic assumption which underlies the doubling dose method but more work along these lines with other species is still required.

In this respect it is worth mentioning here a study of mutation induction in the somatic cells from the mouse, the Chinese hamster and from man (Univ. of Leiden) which revealed a very similar mutation induction rate per rad, with man being slightly more sensitive.

3.5. Repair in mutagenesis and aberration formation

The availability of a range of repair deficient strains in microorganisms has permitted a detailed study of the genetic control of radiation sensitivity. In yeast some repair deficient strains are available and a collection of human cells which exhibit repair deficiencies is also being made. The newly available repair deficient mutant strains of Drosophila will permit an investigation of the role of the repair deficiencies in radiation induced mutagenesis and aberration formation both in somatic and germ cells. This new development in a species with such well established genetics could result in Drosophila becoming a truly classical material for the study of the genetic control of the biochemical pathways involved in the repair of radiation damage.

In a study in which normal male Drosophila were irradiated and mated to either normal or repair deficient females (Univ. of Leiden) it was found that the three different repair deficient strains (mei-9, mei-41, mus-101) influenced the genetic effects studied in different ways. Initial results from experiments where males were irradiated in air, O_2 and N_2 and mated to females of one repair-deficient (mei-9) strain confirm the

suggestion from earlier work that the damage induced in O_2 is qualitatively different from that in air or nitrogen.

In two of these same repair deficient strains a study has also been made of the formation of chromosome aberrations and sister chromatid exchanges (SCE) (Univ. of Rome). Irradiation of larval neuroblast cells during S phase showed that both the mei-9 and the mei-41 mutants were 10 times more sensitive than wild strains for the induction of chromosome aberrations. The pattern of induced aberrations differed between the two mutant strains and it could be concluded that the mei-9 mutant was deficient in chromosome joining. The mei-41 mutant was partially deficient in the functions involved in the formation of chromatid interchanges, especially symmetrical interchanges. The results could be interpreted as indicating that although the formation of exchanges is dependent on the close proximity of chromosomes the type of rejoining is defined at the molecular level. It was also found that SCE formation did not occur spontaneously in Drosophila and the two repair deficient strains had a close to normal frequency of induction of SCE's suggesting that the repair deficiencies, although influencing meiotic recombination and chromosomal aberration formation were not affecting the formation of SCE's.

A study of the sensitivity of repair proficient and repair deficient strains of yeast in different parts of the cell cycle (Univ. of Swansea) revealed that the resistance normally found in S and G_2 was abolished in cultures carrying defective alleles of the RAD50 gene. This led to the conclusion that the gene products of the RAD50 and the close association of sister chromatids are involved in the repair of radiation induced DNA damage in yeast.

3.6. The Molecular nature of radiation damage

An important step forward has been made in the understanding of the basic mechanisms which are involved in the formation of chromosome aberrations.

In a series of elegant experiments (Univ. of Leiden) Chinese hamster cells have been irradiated in G_2 and then treated with Neurospora endonuclease, an enzyme which specifically cleaves single stranded regions in DNA. The rationale behind the experiments was that if DNA double strand breaks are the major lesions which lead to the formation of chromosomal aberrations, the addition of the endonuclease after low LET radiation would convert many single strand breaks into double strand breaks and consequently increase the number of aberrations. After high LET radiation, which mainly induces double strand breaks, the endonuclease should have no substantial effect on the number of aberrations. The Chinese hamster cells were treated with X-rays and neutrons and the results were exactly as expected. After X-rays addition of the endonuclease increased the aberrations by a factor of 3 to 4, after 0.5 MeV neutrons the enzyme had no effect. In addition the number of DNA double strand breaks induced after X-rays with and without the addition of the enzyme has also been determined.

In this experiment addition of the endonuclease increased the number of double strand breaks by a factor 2, comparable with the result of the cytological studies. These results are interpreted to indicate that the "major DNA lesion induced by ionizing radiations which leads to chromosomal aberrations is a DNA double strand break".

In a study of the response of ataxia telangiectasia cells to X-rays, beta rays from incorporated tritiated thymidine and 0.5 MeV neutrons (Univ. of Leiden), it has been found that these cells are more sensitive than normal cells for the induction of chromosomal aberrations. This enhanced sensitivity was observed after irradiation both in G_1 and G_2 phases of the cell cycle. An unusual feature found in AT cells is that, after X-irradiation in G_1, both chromatid and chromosome-type aberrations are recovered. On the basis of these and other results from experiments on post-irradiation treatment of AT cells with caffeine, it has been concluded that (i) compared to normal human cells, AT cells are more sensitive to all types of ionizing radiations tested thusfar and (ii) the defect in AT

cells is probably due to a defect in the repair of DNA strand breaks.

The results of work on the induction of chromosomal aberrations in Vicia faba root tips by long wave UV and by X-rays (in which BrdUrd had been substituted for thymine in various numbers of DNA strands in the chromosomes) have been interpreted as providing direct evidence for the thesis that two lesions are required to produce one exchange (Univ. of Leiden).

The important role of DNA double strand breaks in the biological effects of ionizing radiation was emphasized by work with yeast cells (GSF, Frankfurt). In measurements on lethality and double strand break induction in a repair deficient yeast a consistent association between the number of double strand breaks per lethal event was found after irradiation with electrons or α particles in both oxic and anoxic conditions. It is concluded that 1 to 2 double strand breaks are lethal in these cells and that the double strand break is a potentially lethal lesion in wild type cells. The dose response relationship for initial double strand breaks was found to be linear but in wild type cells is rapidly converted into a linear-quadratic relationship. Wild type stationary cells can repair a large proportion of double strand breaks and it is considered that this repair is responsible for the occurrence of a shoulder on the survival curve. Irradiation of stationary cells at very low dose rates reduced the quadratic component of the double strand break dose response. This led to the conclusion that at high dose rate irreparable double strand breaks are induced by interaction of reparable double strand breaks. The results are interpreted to be "in agreement with the suggestion that repair of double strand breaks involves a recombinational process between two homologous chromosomes in the region of a double strand break".

3.7. Correlation between different biological end-points

Ionizing radiation induces many different kinds of detectable biological end-points, such as lethality, point mutations, aberrations, mitotic crossing-over, non-disjunction etc. and in

many cases the different end-points respond in a qualitatively similar way to changes in radiation quality, dose rate and oxygenation. However, the quantitative association between the different end-points is not so clear cut: some studies appear to indicate a close relationship between the different end-points whereas others appear to indicate a lack of correlation.

A study of X-ray sensitive mouse lymphoma cells (Univ. of Brussels) demonstrated a positive correlation between the frequency of chromosome aberrations and cell lethality. The conclusion that cell killing is almost entirely due to chromosome aberrations is drawn from an experimental and theoretical study of the effects of neutrons and gamma rays on Chinese hamster cells (AERE, Harwell). Quantitative correlations between cell lethality, chromosomal aberrations and mutations in somatic cells have been demonstrated by the analysis of literature data (ITAL, Wageningen). A correlation between mutation rate and cell killing in yeast was found after irradiation with different radiation qualities (Univ. of Giessen) although each radiation type exhibited its own correlation and no single unique correlation was found. A study of cell cycle sensitivity in yeast (Univ. of Swansea) revealed that maximum sensitivity to mitotic recombination coincided with maximum sensitivity to mutation induction and cell lethality and prompted the conclusion that "similar DNA lesions lead to different genetic consequences during the cell cycle". In a study using two wavelengths of UV radiation, quantification of pyrimidine dimer induction and photoreactivation techniques in different cells it has been clearly demonstrated that UV induced pyrimidine dimers in the DNA are responsible for cell killing, chromosomal aberrations, point mutations and SCE's (Univ. of Leiden). The results indicate that after UV irradiation all biological effects studied so far are caused by pyrimidine dimers, even though the numbers of dimers required give rise to different biological effects are different.

In contrast to these results a study using Aspergillus nidulans using fast electrons, X-rays, β-particles and α-particles (PCL, London) indicated different RBE values for different

biological end-points scored, which included chromosomal non-disjunction mitotic crossing over, deletion, gene conversion and point mutations. A comparison of mutation frequencies and chromosome aberration frequencies in the same cells (Univ. of Leiden) indicated different ratios after ionizing radiation and UV radiation suggesting "that simple correlations between chromosome breakage and mutation induction probably do not exist".

In view of the differences between the results and interpretations of the different groups the development of techniques to discriminate between the induction of point mutations and chromosome deletions in mammalian cells (Univ. of Leiden) is very promising and should help resolve the question of the associations between the different end-points induced by ionizing radiation.

In summary all the results discussed in this section 2 can be taken to indicate that common types of DNA damage operated on by comparable repair pathways appear to be responsible for the effects of ionizing radiation in a wide variety of species extending from yeast, Drosophila, Chinese hamster, mouse, monkey and man. A better understanding of the basic types of damage and the repair functions together with more direct information on the effects of radiation on the germ cells of higher primates and man should eventually lead to an accurate assessment of the genetic risk to man from ionizing radiation.

4. DOSE-EFFECT RELATIONSHIPS IN EUKARYOTES

The main aim of the work in this section is concerned with the shape of the dose effect relationship for biological effects induced by ionizing radiation, the extrapolation of the dose effect relationship to low doses and the modification of the dose effect relationship by extraneous factors. This work is important for the understanding of the relationship between effects induced by high dose, acute irradiation and the effects

induced at low dose, chronic irradiation levels and will be of value in the assessment of risks of low doses of radiation in humans.

4.1. Modification of dose-effect relationships

In a study of the effect of oxygen tension on the frequency of chromosome aberrations induced in normal human cells (peripheral blood lymphocytes) (NRPB, Harwell) using X-rays and neutrons it was found that the dose-effect curves could be fitted by a linear-quadratic relationship. The X-ray data indicated that the effect of oxygen was restricted to a range between 10^2 and 10^4 ppm, the yields of dicentrics tending towards constant values at oxygen concentrations above this range. Taken together the X-ray and neutron data showed that the dose modifying theory of oxygen was limited, especially at low doses and the results favoured an effect modifying factor hypothesis for the action of oxygen. The enhancement ratios for oxygen obtained in the normal human cells are in agreement with values derived from animal experiments.

In a study on the effects of non-toxic physiological substances on the dose response for cell killing (Techno, Dublin) it was shown that the cellular metabolic state can have a considerable influence on the radiation response. Modifying effects were obtained with vitamin A, vitamin C, oxygen deprivation, Lactate, Ethanol, prostaglandin E and isobutyl methylxanthine.

4.2. Neutron irradiation and RBE

In an investigation of the qualitative effect of neutrons the rate of lethality associated with autosomal translocations in Drosophila after X-ray and neutron irradiation was studied (Univ. of Leiden, ITAL, Wageningen, TNO, Rijswijk). Neutron and X-ray induced translocations were tested for viability and fertility in homozygotes but no significant difference was found in the ratio lethal : fertile : sterile from the translocations from the two types of radiation.

In a second study Drosophila males carrying a doubly marked Y-chromosome were irradiated with X-rays and neutrons and progeny were scored for losses and duplications of the Y-markers. At the dose levels giving a similar frequency of exceptional progeny the spectra of the exceptional types was the same after neutron irradiation as after X-rays. The rationale behind this experiment came from the fact that X-rays induced both chromosome and chromatid rearrangements in Drosophila spermatozoa and the question of whether the chromosome rearrangements arise from double strand breaks and chromatid rearrangements from single strand breaks. X-rays induce a higher proportion of single strand breaks to double strand breaks than do neutrons and the fact that both irradiations gave a similar result led to the conclusion that chromosome and chromatid rearrangements were not derived directly from double strand breaks and single strand breaks respectively.

More research is obviously necessary to complete the comparison of the qualitative effect of neutrons and X-rays.

In general it has been found that the RBE of a type of radiation compared with X-rays increases at lower doses and this is ascribed to the curvi-linear dose response relationship found after X-radiation. The low dose RBE of neutrons is important for radiation protection. In some cases neutron irradiation has been found to have a very large RBE value at low doses and the measurement of neutron RBE at low doses is of considerable importance to radiation protection.

Using human peripheral blood lymphocytes the yield of dicentric aberrations has been determined after neutron irradiations of different energies, and consequently radiation qualities, and also after α-particle irradiation (NRPB, Harwell). The dose relationship was found to be linear-quadratic, in general, except in the case of fission neutrons and α-particles, when linear dose relationships were obtained. The maximum RBE value for neutron irradiation increased with decreasing neutron energy and a value of 47 was found for fission neutrons. In the case of α-particles the maximum RBE value was 6.

Using stationary Chinese hamster cells and scoring chromosome aberrations after gamma rays and fast neutrons (AERE, Harwell) it was found that the RBE for low doses of neutrons was only 6 in these cells in comparison to a value of 30 found in human lymphocytes by others.

In stationary epidermal cells of Saintpaulia a low dose RBE for fission neutrons of 10 was found when the leaves were cultivated immediately after irradiation (ITAL, Wageningen). However, if cultivation was postponed by 2 days the low dose RBE increased to 35, mainly because the X-rays became less effective due to repair.

In protoplasts of Nicotiana an increasing RBE of neutrons at lower doses was found in accordance with other eukaryotic systems (CEC, Ispra). Fractionation with gamma rays led to a significant increase in cell survival but fractionation with neutrons did not and six doses of 5 rad of neutrons separated by 1 hour produced an effect equivalent to 1200 rad of acute gamma rays. This effect could not be explained by cell progression and indicates again a high RBE for neutrons.

X-rays were found (Justus Liebig Univ., Giessen) to be more lethal in yeast than heavy ions. Effectiveness increases with ion energy and, among ions of comparable energies, with mass.

4.3. The effect of low doses of radiation

In a study making use of the occurrence of uranous outcrops of rock in France a series of different biological end-points have been used in areas of different dose rates of natural radiation (CEN, Mol; INRA, Dijon; Univ. of Toulouse). Using a double heterozygote of Nicotiana tabacum having greenish-yellow leaves reversion mutations of leaf cells to a green colour can be scored, a higher reversion frequency has been found in plants grown over the uranous outcrops compared with plants grown over non-active control sites. The dose response relationship determined for plants grown over sites having different dose rates from 0.3 mrad/h up to 1 rad/h was found to be linear. At

dose rates below 0.3 mrad/h no significant increase over the spontaneous reversion rate was observed.

Using the waxy system in barley pollen grains, it has been found that the frequency of waxy mutants in plants grown over uranous outcrops was significantly higher than that found in plants grown in control sites. At the higher dose rates the dose response appears to be linear but at the lower dose rates the mutation rate appears to become constant at about twice the level of the control plants.

These results demonstrate that low and very low doses of ionizing radiation do have genetic effects.

In a study using rabbits housed in a hut built in an area of high background radioactivity (dose rate of 3 mrad/h) the induction of chromosome aberrations in peripheral blood lymphocytes was followed as a function of the time spent in the hut (CEN, Mol). The results revealed that the incidence of aberrations increased with time up to 8 months but became very variable after longer time intervals. Measurement of the radon concentration in the hut and comparison with a model radon exposure experiment revealed that the increase in aberrations was associated with the gamma radiation and not due to radon exposure. An experiment with male and female mice kept in the hut for the summer period indicated that an estimated external dose of 15 rad at low dose rate raised the fertility of the male mice but decreased that of the female mice.

In an examination of 9.5 day old F_1 mouse embryos for chromosomal structural abnormalities after exposure of the parents to X-rays (Univ. of Göttingen) it was found that only when chromosome banding techniques were used could structural abnormalities be detected. After exposure of the mothers to 20 and 200 rad of X-rays no disturbance in the sex-ratio was found even though 200 rad caused a high level of embryonic lethality. The incidence of translocations after 20 rad was 1.1% and all translocations were unbalanced. The results extrapolated to humans imply that maternal exposure may increase the risk for abortion and also trisomy and monosomy in offspring. The

exposure of male mice with the same doses also gave an indication of aneuploidy in the F_1 generation although a clear cut dose effect could not be demonstrated. The finding of aneuploid F_1 embryos after the exposure of premeiotic germ cell stages to 20 rad is considered to merit further investigation.

Using the S-locus of Oenothera organensis to test for incompatibility-compatibility mutations it was shown (ITAL, Wageningen) that low doses of X-rays and fission neutrons (2.5 - 20 rad) do cause a significant increase in the frequency of these mutations.

In a cytological follow-up study of 42 workers in a Nuclear Power Station (ENEL, Turin) no significant increase in the frequency of chromosome aberrations in the peripheral blood lymphocytes was noted compared with a control group. However, a slight increase in acentrics and an occasional ring or dicentric was observed in the power station workers. The ring chromosomes were found in individuals who had accumulated more than 20 rem and the dicentrics in workers who had accumulated more than 35 rem. A 5 year follow-up study of 25 individuals showed that in 70% of the subjects the aberration frequency had increased, in 15% it was the same and in 15% it had decreased. These findings suggest that in individuals exposed chronically to low levels of ionizing radiation a biological effect may be detected using the cytological techniques.

The results summarized in this section demonstrate clearly that very low doses of ionizing radiation can cause genetic effects in somatic and germ cells and provide some support for a linear dose effect relationship at low doses with no threshold. The results also demonstrate that the radiobiological effect of neutrons is very poorly understood and that neutrons might be extremely effective at very low doses. It appears that the re-estimation of neutron and gamma ray doses to the A-bomb survivors may also make it necessary to learn much more about neutron radiobiology. It is obvious that much more work in these topics is necessary to broaden the basis for the assessment of the risk to man from low doses of electromagnetic and neutron radiation.

SECTOR F

EVALUATION OF RADIATION RISKS

1. PURPOSE AND GENERAL VIEW

The aim of the research conducted in the field of the evaluation of radiation risks is the development of methodologies for the evaluation of the consequences of the irradiation of populations. These methodologies are a prerequisite for implementing the Community Directives and the recommendations of the International Commission on Radiological Protection, particularly with regard to the justification of exposure and the optimization of radiological protection.

The present state of knowledge does not enable to set thresholds for the effects of ionizing radiation on the health of man. It therefore is necessary to have at our disposal, for each possible source of exposure, ways to evaluate the levels of exposure to individuals and to groups of the population; the resulting radiological detriment and the economic and social consequences of irradiation.

Mathematical models for evaluating individual doses as a function of releases of radioactivity into the environment have been established and only an updating for some radionuclides (e.g. plutonium and transuranics) has to be carried out. It is much more complex, however, to evaluate the collective dose as it is an integration of the individual doses for a given population. It is therefore necessary to consider the migration of radionuclides in the environment, as well as their incorporation in the food chain. For the determination of the dose distribution within a population, other parameters such as the geographical distribution of the sources of pollution and of the population, also have to be taken into account.

The evaluation of the detriment to human populations requires knowledge on the dose-effect relationship. Endeavours must be made to devise methods for defining, or at least, arriving at an approximation of these relationships in the cases of exposure to small doses resulting from the normal operation of nuclear plants and to higher doses resulting from accidental releases. Therefore, epidemiological research, experimental studies with animals and theoretical studies on modelling and synthesis are required.

The optimization principle of radiological protection can be implemented through different approaches, the final objective being a choice of technical options resulting in exposure levels being as low as reasonably achievable (ALARA principle), economic and social factors being taken into account. The recommended cost-benefit and cost-effectiveness analyses are not exclusive, and other decision-making methodologies developed for other purposes can be applied for radiological protection. The advantages and disadvantages of theses methods are investigated.

The following chapters give a synthesis of the results obtained along these lines of investigation. This research was carried out by the Association Euratom-CEA at Fontenay-aux-Roses, France and by its sub-contractors. The latter were entrusted with the study of topical problems within the field of their specialization.

2. METHODS FOR THE EVALUATION OF INDIVIDUAL AND COLLECTIVE DOSES RESULTING FROM NORMAL DISCHARGES AND ACCIDENTAL RELEASES

Application of the dose limitation system recommended by ICRP (Publication N° 26) requires the evaluation of individual and collective doses from all sources, in particular potential doses liable to result from the operation of nuclear installations. The studies conducted relate exclusively to methods for the evaluation of individual and collective doses resulting from normal discharges and accidental releases. Placed in the context of the European Community, the approach leads to the definition of applicable criteria, according to an outline being:

- systematic by a standardized and homogeneous representation of the data and the results;
- objective, by the choice of assumptions taken into consideration in the calculations (whether the latter relate to the location of the sources, the assumptions concerning discharges or other factors) or the choice of the methods of resolution;
- general, by the search for models that, with appropriate parameters, can be used in different situations and by performing application exercises, enable to test the sensitivity of the results to these parameters.

The results obtained therefore constitute a contribution to the constitution or extension of data banks harmonized at an European level (comprising meteorological, demographic and economic data), on the one hand, and on the other hand to the development of dispersion, transfer and exchange models intended to supplement existing models and either to narrow-down or to extend their range of validity by having recourse, if necessary, to experimental studies. These data and models can be used for the application of the Directives of the Commission of the European Communities relating to discharges of radioactive effluents that are liable to affect other Member States (Article 37 of the Treaty).

As the aim of the evaluation of collective doses is essentially to evaluate the detriment, the methods described are not limited to a computation of the overall collective dose, being nothing more than the integration of the individual doses, but also make it possible to study the distribution of the latter over the population, particularly revealing the extent of the range of variation of the individual doses, the theoretical maximum being represented by the critical dose to the individual. The distribution of the doses within a range of increasing levels provides indications that are extremely useful in evaluating the detriment and could prove to be indispensable whenever the assumption of the linear dose-effect relationship without threshold may be questioned.

2.1. Methods for the evaluation of the radioactive contamination of the physical environment

2.1.1. Atmospheric dispersion

Evaluation on a European scale of the radiological consequences of gaseous discharges in normal and accidental conditions requires the use of an atmospheric transport model applicable over a radius of several hundred kilometers. A study of the existing models has demonstrated that the scope of the latter was insufficient for such an evaluation. The MESOS model (Imperial College of Science and Technology, London, UK) is a trajectory model based on actual meteorological data. Each puff of radioactive substances evolves according to the initial conditions at the point of release and the conditions prevailing throughout the distance covered at a given time interval. In the vicinity of the source, the vertical dispersion is based on the diffusion parameters of a Gaussian plume until the height of the mixing layer is reached; thereafter, further dispersion depends on the variations in height.

The diffusion and the evolution of the concentration of the pollutant in the atmosphere are calculated on the basis of actual data for each of the puffs, which are released at regular intervals, the chosen interval of three hours seeming to be satisfactory. The results are recorded within the meshes of a grid covering the European territory. The consecutive concentrations for a given duration of discharge can be obtained by integration of the results relating to the corresponding trajectories, but the number of sites for which a calculation is carried out depends on the problem under consideration. The results are expressed either as time integrated concentrations per unit of activity released (in the case of short discharge) or as average concentrations per rate unit of activity released (in the case of a continuous discharge). The model was tested on the Windscale accident and, taking into account the poor meteorological data, its validation proved to be satisfactory.

For operational discharges uniformly distributed throughout the year, five locations on the territory of the European Community were chosen as hypothetical discharge sites: this choice was inspired by the concern to acquire the best possible set of data and to obtain a good representativity with regard to geographical characteristics. For each site the isoconcentration curves are plotted in the grid meshes corresponding to the meteorological data base used.

Application exercises showed that for a given element, the shape of these curves, due to preferential trajectories of the pollutants, proves different not only according to the site (e.g. Mol and Cadarache) but also, for a given site, according to the year considered (e.g. Mol, 1973 and 1976). The health implications linked to these differences in distribution vary according the pathways of exposure of the population.

2.1.2. Aquatic dispersion

The modelling of the migration and difusion of effluents in the aquatic environment poses problems as complex as those which arise when considering releases into the atmosphere. Attempts were made to define the scope of these problems or to specify their relative importance with regard to the possible radiological impact on European populations of discharges into the sea.

As regards the evaluation of average concentrations in seawater, checks were made to determine whether there was satisfactory agreement between the computed results of a compartment model and the measured results in the case of known discharges. The parameters of this model will have to be specified for the behaviour of transuranics which are subjected to physico-chemical transformations as a function of the properties of the environment. An experimental study has underlined the fundamental importance of the pH of reconstituted sea-water on the physico-chemical form of plutonium-VI (Département de Chimie Appliquée et d'Etudes Analytiques, CEA, Fontenay-aux-Roses, F).

Using a set of arbitrary contamination assumptions serving as input data for an exchange model in seafoods, the influence of the level of radioactive contamination of the water in various fishing grounds on the ingestion of radionuclides by consumers was tested. The combined effect of the intensity of fishing the grounds and of their distribution was underlined (Association Euratom-CEA, Fontenay-aux-Roses, F). Attempts were made, through the combined application of the compartment model and the exchange model, to draw a comparison between coastal discharge sites presenting considerable differences in transfer. The overall impact of such discharges, compared with that of atmospheric discharges, is small since it is limited to a few radionuclides (Association Euratom-CEA, Fontenay-aux-Roses, F).

Evaluation of the results leads to suggest the use of a relatively simple model for the overall and average evaluations and the use of site specific models, taking into account the physico-chemical and biological phenomena as well as the conventional diffusion equations, for particular studies. Further justification of this approach is provided by the possibility of interactions between the marine environment and the atmosphere, which may be important in the case of direct exposure.

2.2. Methods for the evaluation of the radioactive contamination of food products

Once a certain level of radioactive contamination of the physical environment is reached, the population can be exposed through various pathways, namely direct exposure to radiation, the inhalation of contaminated air and the ingestion of contaminated water and foodstuffs. One of the most complex problems is that posed by transfers to man via vegetable and animal products. Models have been developed and suitable values were assigned to the parameters in order to evaluate the transfer of radioactivity between the physical environment (air, water and ground) and the main animal and vegetable products consumed by man. The knowledge available in this area has been reviewed, interpreted and supplemented in a number of aspects that are particularly important for the objective pursued.

2.2.1. Deposition rates and retention coefficients

The choice of the values to be introduced into the models should be well-adapted to factors such as the distance considered from the point of release, the need to evaluate both the amounts deposited on the ground and the attenuation of the plume, the type of discharge (normal or accidental, short or prolonged) and the type of pollutant. The variability of the values available in the literature renders such a choice difficult and prompted, in the case of iodine-131, a reappraisal of the experimental results previously obtained in situ.

A new statistical analysis revealed the nature of the distribution of the iodine concentration on grass and the importance of certain biological parameters, in particular the density and water content of grass (Association Euratom-CEA, Fontenay-aux-Roses, F). In addition, a series of experiments conducted in the laboratory has demonstrated the influence of atmospheric humidity on the uptake of elementary iodine by vegetables (Département de Chimie Appliquée et d'Etudes Analytiques, CEA, Fontenay-aux-Roses, F). Finally, a semi-empirical relationship between the rate of deposition on grass and climatic factors (temperature, humidity and wind speed) has been put forward and the parameters of this relationship have been evaluated in the case of iodine. Such a relationship offers a possibility for producing a realistic estimate of the deposition and the attenuation of the plume in relation to the atmospheric conditions prevailing during the discharge (Association Euratom-CEA, Fontenay-aux-Roses, F).

2.2.2. Washout coefficients

Following a critical literature review, an expression of this coefficient in relation to the rain intensity has been proposed. As in the case of the deposition rates, the sensitivity of the results to the value of the parameters has been evaluated (Association Euratom-CEA, Fontenay-aux-Roses, F).

2.2.3. Factors influencing the transfer from the physical environment to the food chain

The effort in this field mainly consists in a critical study of the transfer parameters of the transuranics (neptunium, plutonium, americium and curium). After having reviewed the nuclear and physico-chemical properties of these elements that affect their behaviour in solid and aqueous environments and their transfer to vegetables, tables of the values of the various parameters were made which revealed both the great variability of the latter and a large number of gaps (Association Euratom-CEA, Fontenay-aux-Roses, F).

2.3. Methods for the evaluation of doses to the population, socio-economic data and exchange models

The dose limitation system recommended by ICRP leads to an evaluation of both, the individual doses and the collective and average doses to the population. In view of the number and the diversity of the pathways of exposure, it is necessary to have data and models enabling to test for real situations the relative importance of the parameters and the validity of any simplifying assumptions.

A European grid has been designed and specified for recording, adapting and exploiting the various data required for dose evaluations, namely :

- meteorological data presented on a grid of geographical coordinates;
- demographic data concerning nine of the Member States of the European Community and Switzerland classified according to the geographical coordinates of the localities;
- information on agricultural products, prepared for the CEA-NRPB study (Methodology for evaluating the radiological consequences of radioactive effluents released in normal operation), was supplemented or updated at the application stage.

These three sets of data are represented on a grid with mesh dimensions as a function of the data treated. Such data, which are available on computer tape, are suitable for calculating the ambient concentrations, the distribution of the inhalation doses and external radiation doses and the distribution of the radioactive contamination of agricultural products.

Treatment, processing and storage of and trade in products before their consumption can affect to varying degrees the levels of exposure of populations and the distribution of the doses within these populations. In order to evaluate these effects, an exchange model based on the analysis of economic information has been developed, for taking into account the dilution factors prior to an estimation of the doses to the populations. Examples of both, agricultural products and seafoods, have been calculated (Association Euratom-CEA, Fontenay-aux-Roses, F).

2.4. Application exercises

The aim of the exercises is to test the application of the models for evaluating collective doses using existing data bases of Member States. The method of representation of the results enables to observe differences in the dose distribution received from an identical source through various pathways.

2.4.1. Distribution of the collective doses in the case of direct exposure (external irradiation and inhalation)

Five release sites on the territory of the Community for which a highly satisfactory set of data exists were chosen, namely Mol, Heysham, Karlsruhe, Cadarache and Ispra. The discharges are assumed to be continuous and uniform. The resulting collective doses on the territory of the European Community were evaluated by using the European population distribution model based on the data of national censuses and by using conventional models for the evaluation of individual doses derived from atmospheric concentrations. The

collective doses are evaluated for each large mesh of the above defined European grid. This calculation enables a mapping of the distribution of collective doses from each release point, which provides an extremely useful reference document for the study of the potential risks and their geographical distribution related to the site of release. The value of the resulting collective dose in a given area, when related to a unit of activity released, gives a correct distribution of the risk for the area under consideration (Imperial College of Science and Technology, London, UK and Association Euratom-CEA, Fontenay-aux-Roses, F).

The evaluation of the dose received within a given perimeter around the release site expressed as a percentage of the total collective dose, makes possible to determine the boundaries of the area beyond which the dose values become so low that it is useless to take them into consideration. If the ratios of the collective doses to the number of persons concerned within a given perimeter around a site of release are considered, it is clearly seen that these ratios do not increase and even tend to decrease when, while moving away from the site, the surface of the territory concerned and the population increase. The effect of atmospheric dilution over long distances therefore predominates over the effect of the size of the population. (Association Euratom-CEA, Fontenay-aux- Roses, F).

2.4.2. Distribution of the collective doses in the case of indirect exposure (ingestion)

2.4.2.1. Contribution of the different zones of production to the collective dose

The mentioned MESOS model enables to calculate both dry and wet deposition. In the latter case, it uses meteorological precipitation data codified according to the intensity and duration of the precipitation. Based on these depositions, the specific activity of the various agricultural products and the overall levels of activity transferred to food products can be calculated, provided that the distribution of the production of food products in the zone concerned

is known. For the applications studied, an existing map of the distribution of agricultural products in the different meshes of the European grid was used. The amounts of Cs-137 and I-131 transferred into the different products and their distribution from a unit discharge were calculated. Such an evaluation integrates climatic factors, transfers in the environment and food production. The case studies demonstrate that the variability of the contribution, in terms of both value and percentage, of the various agricultural products originating from zones surrounding the site of discharge differs substantially and is is often greater than that of direct irradiation. The influence of site-specific characteristics is very marked in the case of the contamination of agricultural products and for a given site, the contribution to the collective dose by contaminated agricultural products, which is closely linked to the meteorological conditions, is subject to a year-to-year variation much larger than the contribution of external irradiation or inhalation (Association Euratom-CEA, Fontenay-aux-Roses, F).

2.4.2.2. Distribution of the collective doses at a consumers level

After evaluation of the contribution of the zones of production to the collective dose, it appears important to study the distribution of this collective dose between the consumers of contaminated products. Application exercises of the exchange model mentioned before provided information with regard to the distribution of the collective dose at a regional level. It must however be pointed out that the delimitation of the regions adopted in administrative and statistical documents varies according to the type of product, for reasons connected with production or collection constraints, processing capacities or compliance with certain trading agreements. It is therefore necessary, in order to obtain for all the pathways of irradiation a homogeneous set of results linked to a given source of pollution, to carry out an adapted distribution. In this way, the matrices for the transfer between meshes of the grid are created based on the matrices for transfer between regions. The case study of bovine meat, a potential vector for Cs-137, illustrated the effect of trade on the distribution of the doses (Centre d'Evaluation de la Protection dans le domaine Nucléaire, CEA, Fontenay-aux-Roses, F).

2.5. Conclusion

The developed methodologies can be used for several purposes. In the case of continuous, uniform discharges resulting from the normal operation of installations, these methodologies enable to establish:

- forecasts of the potential irradiation hazards to populations from planned discharges
- comparisons between potential sites of release
- balance-sheets of the irradiation of populations from practised and monitored discharges from one or more sources.

In the case of accidental releases, these methodologies can be used for :

- evaluating the potential hazards resulting from a hypothetical situation, e.g. the reference accident.
- evaluating the consequences of actual accidental releases, whether concerted or not.

The MESOS model is suitable for estimating trajectories and for calculating integrated atmospheric concentrations, either under conditions that are known (or assumed to be known) or in terms of the probability of given levels being reached at certain points.

Knowledge of the transfer mechanisms or the parameters governing deposition and retention of radionuclides in relation to the climatological environment, mainly during the discharge, is extremely important if the contamination of food products is to be evaluated correctly. The results of these studies can be useful for the study of cases that are precisely defined with regard to both, the site and the release conditions: they may lead to a choice of different values of the averages in the case of continuous discharges.

The exchange models of food products constructed with annual production data and average transfer factors could be used for forecasting the consequences of a prolonged, wide-ranging contamination possibly caused by an exceptional discharge of a long-lived radionuclide.

3. METHODS FOR THE EVALUATION OF THE RADIOLOGICAL DETRIMENT TO MAN

Evaluation of the detriment resulting from the irradiation of human populations requires knowledge of the relationship between dose and effect in the case of man. The aim is therefore to seek methods for defining or, at least, arriving at approximations of these relationships.

A considerable amount of knowledge on the biological effects of ionizing radiation has been accumulated over the last three decades. The concepts of non-stochastic effects, whose severity is a function of the dose with the existence of a threshold, and of stochastic effects of probabilistic type with the implied absence of a threshold, are currently well-estbalished from a qualitative point of view. From a quantitative point of view, the evaluation of the risk resulting from low doses presents serious difficulties and still gives rise to a number of discussions of methodological nature.

The main difficulty resides in the fact that the stochastic effects of ionizing radiation (malignant diseases and genetic disorders) do not have a specific characteristic: the clinical expression of radiation-induced cancers or hereditary defects is identical to those induced by other carcinogenic or mutagenic agents in the environment. A relationship between the dose absorbed by a living organism and a given effect can therefore be studied only by looking for an increase in the incidence of that effect in comparison with its "natural" frequency.

Epidemiology and animal experimentation constitute the two main approaches for conducting the analysis. Their respective advantages and disadvantages differ to such an extent that they can be considered complementary. While animal experimentation can contribute to the shaping of theories, it is always necessary to verify their validity in the case of man and to undertake epidemiological studies.

3.1. Epidemiological studies

Defined as the study of the distribution of illnesses and invalidities in populations and of the parameters which determine that distribution, epidemiology has a descriptive aspect that makes it possible to put forward hypotheses and an analytical aspect that endeavours to identify the complex features of the etiology of the illnesses under consideration. It is therefore not simply the application of statistical methods to public health. Special attention is given to the procedure used and to the logic of the interpretation. In the field of radiation protection, the continuous questioning of the validity of the extrapolation of data from animal experimentation to man renders epidemiology of the highest interest.

Most of the knowledge acquired on the biological effects of high doses is the result of epidemiological surveys. The evaluation of the radiological detriment due to low doses is much more difficult to conduct with this approach. Two methods are frequently used to estimate the hazard due to the exposure of human populations to ionizing radiation:

- first, the method involving surveys with control cases, still called the matched pairs method, in which the frequency of the determining factor(s) that are likely to be the cause of a pathology is compared in two populations, matched in such a way that they present the maximum number of common characteristics (age, sex, socio-economic factors, habitat, etc.), with the exception of the pathology under consideration;
- secondly, the cohort method, still described as prospective, but which can take in certain cases the form of retrospective study. This method entails to monitor over a period of time the state of health of populations that are matched except for the suspected etiological agent, i.e. an exposed and a non-exposed population.

The two methods supplement each other usefully: the survey with control cases enables a quick and economical check of the validity of a hypothesis, while the cohort method gives a more accurate estimate of the risk since it enables to calculate the ratio of the number of subjects affected to the number of subjects exposed and consequently to estimate the risk.

The guidelines for the methodological research were set after carrying out a literature survey. Knowledge about the genetic effects of ionizing radiation on pluricellular eukaryotes was reviewed (University of Leiden, Leiden, NL): evaluation of the genetic risk to man was considered in the light of recent acquisitions in view of eliciting information from research currently conducted in the world and suggesting new fields of investigation. In the same context, a critical study of the bibliographical data on the somatic effects of ionizing radiation, with a special effort to update the UNSCEAR 1977 data, was carried out in order to determine whether or not it was advisable to undertake epidemiological studies in this area (Research Institute Mario Negri, Milano, I).

There are relatively few situations in which the exposure of human populations enables the implementation of risk studies; most of the cases that can be exploited relate to medical exposures, since radiation used in diagnosis and therapy constitutes the greatest source of the exposure of the general public. The rapid development in radiology during the first half of the century, particularly the frequent use of X-rays in the treatment of a large number of benign illnesses, gives scope for "retrospective" cohort studies: the evolution of the health of groups of subjects exposed several decades ago is monitored a posteriori and relatively reliable dosimetric reconstitutions can be made on the basis of radiotherapy files. A good number of epidemiological studies have been conducted in this area.

The development of the epidemiological approach has been continued in this context of methodological research, while endeavouring to attain the following aims:

- to select populations that are sufficiently large to enable a study of the relationship between dose and effect in the case of dose levels absorbed by individuals that are as low as possible or at least lower than those described in existing surveys.
- to increase the observation periods by isolating the groups exposed three or even four decades ago.
- to attempt to take account of the effect of the other carcinogenic factors in the environment.

Following recent studies that demonstrate a significant increase in the frequency of malignant diseases of the head and neck, in particular cancers of the thyroid, the brain and the salivary glands, in patients irradiated during their childhood for tinea of the scalp, a survey of this type has been undertaken on 10.000 subjects treated for skin diseases of the face (Medical Social Research Board, Dublin, IRL). The main aim of the survey is to evaluate the long-term consequences of the exposure of the thyroid to low doses and of the salivary glands to moderate doses, some 30 or even 40 years after the radiation therapy took place. The method used - that of a retrospective incidence study - is carried out in several stages. The first stage involves identifying the population studied, by gathering all the information concerning the diagnosis, the type of radiation used, the dose given, the number of treatments, etc. In the second stage, the doses to the tissues and organs under consideration are evaluated. The patients treated have then to be followed in order to register those subjects suffering from cancers, those who deceased and those still alive. Finally, the results are analysed by comparing the frequency of cancer in the population exposed to the hazard to that observed in the population at large. A study of this type should make it possible to establish the relationship between the dose given and the cancers observed and, at a later stage, the dose-effect relationship between the tissue dose and the respective cancers.

The main difficulty encountered resides, as was stated earlier, in the coexistence in the environment of other factors that are liable to bias the results when they cannot be eliminated. With a view to evaluating the extent to which such factors exert an influence on the carcinogenic effects of radiation, a study has been undertaken in order to investigate the effects of smoking on populations subjected to exposure for medical purposes (St George's Hospital, London, UK). The aim of the study was to inquire into any interaction between diagnostic radiation and tobacco consumption in the induction of lung cancer. The retrospective cohort method is used. Three cohorts of 30.000 persons have been identified and studied. The analysis of the results is in progress. In practical terms, this study seems to suggest that the concept of the dose-effect relationship as established at present for radiation exposure should perhaps in future be replaced by that of a multi-factorial relationship considering a number of concurrent factors.

3.2. Additional studies

The surveys that have been conducted on the variations in natural background provide a contribution to the difficult problem of the choice of a control population in epidemiological surveys. The relatively good knowledge of the long-term effects on human health of exposure to medium or high doses of ionizing radiation (approximately 1 Gy and above) is largely due to the diversity of the exposure situations that can be or have already been exploited epidemiologically for the purposes of establishing the dose-effect relationship; the literature abounds with examples of this type and the studies presented in the preceding section demonstrate the possibilities in this area.

Estimation of the radiological detriment caused by low doses makes it necessary to examine larger population samples since the effects are small; at very low doses - from around 0.01 Gy to about 0.1 Gy - this requirement becomes practically impossible to satisfy because of the limits on the validity of statistical comparisons and the considerable difficulties in constituting or detecting specific cases for study. In

statistical terms, the predictable additional risk due to low doses (as can be obtained by extrapolation from the results observed with high doses) seems difficult to detect in view of the magnitude and variations of the residual risk in the population. In other words, it may appear illusory to attempt to attribute to low doses of ionizing radiation a limited cancer rate that is in all probability lower than the spontaneous variations in the incidence observed in a non-exposed population. Such fluctuations, which are dependent upon a large number of carcinogenic factors present in the environment, pose the problem of the choice of a suitable control population that differs only by the irradiation variable. Such considerations of the statistical significance of the differences and of the validity of the controls selected constitute the two major stumbling-blocks in the experimental verification on man of the assumptions relating to the estimation of low doses of ionizing radiation.

3.2.1. Natural background radiation

The study of populations subjected to various levels of natural background radiation can be envisaged by ensuring that samples are of the size necessary for observing the predictable effects of low doses (the scale of a million individuals), but it is not possible to establish a cause-effect relationship without checking the different carcinogenic factors in the environment, which are generally more powerful (smoking, alcohol, socio-economic conditions, professional factors, etc.). This consideration may explain the contradictory results of the existing surveys, several of them describing a positive correlation between natural background irradiation and cancer whereas other studies do not observe any correlation.

Other studies point to lower frequencies of malignant diseases in the regions where background radiation appears to be higher, thus highlighting the secondary role of low doses of ionizing radiation in the induction of cancers and the need to tackle the problem as a whole. Furthermore, a number, if not all, of these studies take into consideration only a fraction of the natural sources of radiation, essentially the external sources in the environment and only sometimes

those connected with indoor exposure. The failure to take account of the other components and more particularly radon and its short-lived daughter products is liable to introduce a further bias, falsifying both qualitatively and quantitatively the levels of exposure selected for the study. Any attempt to establish a cause-effect relationship or a dose-effect relationship in the case of exposure to natural background radiation should therefore be based on a systematic account of all the sources or at least on one or more indicators representative of the latter. Natural irradiation was studied in France, Brittany (Association Villermé, Rennes, F) and in Ireland (Trinity College, Dublin, IRL). In both regions, the total annual mean individual dose by external irradiation is about 0.77 mGy. Indoor irradiation appeared to be 25 % higher, namely 0.97 mGy per year. The indoor radon concentration varied appreciably depending on type of building, construction materials and climatological conditions, but no causal relationships could be established. Both studies indicated the necessity of more extensive data collection on indoor irradiation.

3.2.2. Occupational exposure

Likewise, the conditions required for implementing epidemiological surveys were examined in various other situations of exposure to low doses. Recent studies on the health of professionally exposed workers in nuclear installations have been the subject of interpretations that are at least complex and contradictory. The improvement of the basic data available in this field will without doubt contribute to the solution of these problems. With this in mind, a study of the methods for monitoring workers professionally exposed to ionizing radiation was undertaken in view of assessing the possibilities for setting up a registration scheme in the Member States of the European Community.

This study gives an overview of the dosimetric and health data currently available and underlines the difficulties of harmonizing and coordinating data at Community level (St George's Hospital, London, UK). The study of these different categories of information and of that resulting from current research (records of the irradiation of the population for medical purposes) and the presentation thereof on

the European population distribution grid described in section 2 is conducted with a view to compiling an overall catalogue of the different components of the exposure of the population and possibly using it for health comparisons.

3.3. Experimental studies

Animal experimentation becomes indispensable as soon as the object is to deepen our knowledge of the influence of the various parameters of exposure, such as the dose rate or dose fractionation, the quality of the radiation, or the evaluation of the combined effects of various agressions. As in the case of the studies on man, the aims of the research were defined by means of a previous literature review. Emphasis was laid on the areas in which human data are insufficient.

A review of animal data relating to the effects of the ingestion of caesium, plutonium and americium was accordingly carried out in order to contribute to the improvement of our knowledge of the health effects of a possible exposure of man to these radionuclides. The experimental research focused on two main areas: the evaluation of the short-term effects of heavy doses and the study of the long-term effects in animals that survive the initial phase of an acute irradiation and in those that have been exposed to lower doses. The aim of this work is to gather information on the induction of malignant diseases for extremely varied exposure conditions, such as overall neutron and photon irradiations, inhalation of alpha- or beta-emitting radioelements and oral administration of actinides or of fission products (Service de Radiopathologie et de Toxicologie Expérimentales, CEA, Fontenay-aux-Roses, F).

This work is being conducted in conjunction with a study of the combined effects of various carcinogenic and non-carcinogenic chemical agents in order to simulate as realistically as possible the conditions of human exposure. Such a simulation by means of animal experimentation of situations in which man is exposed to ionizing

radiation constitutes an additional approach to the evaluation of biological detriment. In particular, it gives perspectives for the comprehensive study of the mechanisms governing carcinogenicity and it is therefore of special value.

A synergism was observed between chemical products and irradiation whenever the chemical was administered after irradiation. The effects of the inhalation of alpha-emitters on lung carcinogenicity were studied (University of Oxford, Oxford, UK). Exposure of rats to radon and other cofactors revealed strong synergism with cigarette smoke whereas previous exposure to enhanced SO_2 levels reduced life expectancy. Another study compared radiation induced lesions of the kidney of rat and man (Hôpital Necker, Paris, F). The difference of frequency of macroscopic anomalies of the tissue of the kidney of different lines of rats seems to be linked to a genetical predisposition.

Analysis of the large number of gathered data demonstrated that a number of criteria had to be satisfied in order to make data reliable for modelling purposes. These criteria are now considered in the preparation of experimental procedures and those results may be used in constructing a model of carcinogenicity.

3.4. Conclusion

The evaluation of the radiological detriment is a highly complex problem. While the relationships between dose and effect are fairly well known for higher doses (over 1 Gy), they remain to be defined in the case of low doses. Furthermore, in practice only the simplifying assumption of the linear relationship without threshold is still accepted today. The use of approximation methods, which have been briefly described above and some of which have been applied in the fields of both epidemiology and animal experimentation, require substantial programmes of long and difficult work. It is therefore of the utmost importance carefully to study the conditions of such work that are essential for the statistical processing of the data.

With regard to epidemiology, progress in perfecting the methods can be expected from the studies in progress. It appears that the coexistence in the environment of a large number of cofactors is prompting to replace the simple relationship between dose and effect by a multifactorial relationship taking into consideration the factors that act concurrently with irradiation in determining the resulting effect.

Animal experimentation makes it possible to determine precisely and reasonably quickly the influence of the various parameters that are liable to exert an effect: not only the dose, but also the dose rate, the type of radiation involved, etc. When conducted properly according to a strict procedure that gives due regard both to statistical requirements relating to the size of samples and to the problems raised by the risks of introducing a bias of any kind, animal experiments should provide data that can be exploited for developing a theoretical model of carcinogenicity, thus preparing the way for an attempt to extrapolate animal experimental results to man.

4. METHODS FOR THE EVALUATION OF ECONOMIC AND SOCIAL CONSEQUENCES OF IRRADIATION

The dose limitation system recommended by ICRP comprises not only indiviudal dose limits but also the concepts of the justification of exposure and the optimization of protection. In other words, the levels of protection chosen for a given situation must satisfy these three requirements. The so-called "optimization" procedure is the most delicate to put into practice since it presupposes, when passing from a given level of protection to a higher level, the necessity of evaluating in comparable terms the differential cost of protection, on the one hand, and the differential cost of the detriment, on the other hand. Such an evaluation must take account of the monetary value of the economic and social consequences of irradiation, i.e. the "cost of the man-sievert". This encounters a major difficulty since it necessarily refers to the monetary value of human life, the choice of which is of course arbitrary. This leads to a very wide range of values used in the literature.

In order to overcome the difficulties inherent to the cost-benefit method, fundamental research has been directed towards other decision-making methods better adapted to the objective pursued, namely to determine for a given situation the technical options which result in levels of exposure that are "as low as reasonably achievable, economic and social factors being taken into account" (the ALARA principle).

4.1. The different steps of the optimization process

There are generally a number of technical options for radiation protection with regard to a given installation or situation. Once these options have been identified, it is necessary to make a selection in order to identify the "best", i.e. the most effective. The selection shall not, however, take into consideration those compulsory options that are essential for complying with the individual dose limits. Once the best options have been selected, the criteria of comparison to be taken into account have to be identified.

An initial criterion to be adopted is that of the theoretical health effects resulting from residual radiation. These effects are evaluated in the light of the currently available dose-effect relationships, which gives a satisfactory criterion for assessing the effectiveness of these options. The order of magnitude of the hazards evaluated in this way is such that it does not seem worthwhile to take account of the "indirect consequences" connected with the radiological impact of nuclear installations, such as the increase of the need for health care, the incidence on the productivity of undertakings, etc. The direct cost incurred by the undertaking, in the majority of cases, constitutes a sufficient indication of the economic impact of radiation protection options. The nature of the groups of the population exposed is another criterion to be taken into consideration. Distinction should be made between the exposure of workers and that of the general public, the exposure of the critical group and that of the population as a whole and, within the latter, the population of the country concerned and that of other countries.

Once the comparison criteria have been selected, the following step is the evaluation in monetary terms of the consequences arising from each of the options. In the optimization procedure this is carried out by the cost-benefit or cost-effectiveness method, which necessarily involves a value of the human life. In certain cases it is sufficient to estimate the hazards in physical terms, for example in terms of individual doses and collective doses, or, if more precision is desired, in terms of somatic or genetic health effects. The following informations are available at this stage of the process: the radiation protection options selected and their socio-economic impacts, in physical and possibly also monetary terms. The cost of each of the options selected has to be evaluated before envisaging their direct comparison. Such comparisons may be carried out using the cost-benefit and cost-effectiveness methods recommended by the ICRP. Among the other appropriated methods, the multicriteria method and the utility function method seem to be the most suitable for the problem of the optimization of radiation protection.

The multicriteria method is based on the "outclassing" concept. When the best options have been determined, the consequences thereof are evaluated using two indices - a "concordance" index and "discordance" index - making possible the establishment of an order of merit between them. The order of merit is established according to various criteria. The outclassing is deemed to be total when one option dominates another whatever the relative importance of the criteria may be. Certain criteria may, however, be considered more important than others; in that case, the criteria are weighted according to the cost of protection, the collective and individual hazard and the relative uncertainty of the data. An order of merit is thus established between the options based on the criteria adopted. An application exercise of this method compared some 40 procedures for the treatment of gaseous and liquid effluents of nuclear plants and demonstrated the multidimensional character of the choices to be made (Association Euratom-CEA and Centre d'Evaluation de la Protection dans le domaine Nucléaire, Fontenay-aux-Roses, F).

The utility function method consists in determining the "partial utility" linked to each option and in aggregating the latter by summation or multiplication. The options to be selected are those whose combination results in the maximum "overall utility". In the example that was studied, the partial options were defined by their cost and their influence on the collective risk to the public, the collective risk to the workers and the maximum individual doses to the critical group. Application of this method to the effluent treatment systems indicated that certain treatment systems induced an increase of the occupational collective dose exceeding the decrease of the collective dose to the public (Centre d'Evaluation de la Protection dans le domaine Nucléaire, Fontenay-aux-Roses, F).

4.2. Comparison of the different methods of optimization

The cost-benefit, cost-effectiveness, multicriteria and utility function methods were compared by applying them to a single numerical example. Each method has its advantages and disadvantages and the choice of the method depends on the objective pursued and the characteristics of the problem being tackled. For operations in which the criteria of choice are complex and require to take into consideration heterogeneous viewpoints, the multicriteria method offers indisputable advantages.

Whatever method is used, a relative weighting of the criteria cannot be avoided. The comparison of the cost of protection and that of the health effect avoided poses the problem of the value of human life or, of determining the cost of the man-sievert. Two approaches are possible for arriving at this value: the first is an economic approach comprising a combination of the costs of medical treatment and of lost production, the second is an "a posteriori" approach based on the "implicit costs" of the health effect avoided, the latter being calculated on the basis of the costs incurred in the nuclear industry or in other industrial sectors.

4.3. Comparative studies

Evaluation of the implicit costs of the health effect avoided leads to comparisons between the values obtained for different activities or different installations. A first study considered conventional and nuclear electricity generating plants. The annual cost of protection per kWh produced of the oil-fired plants was higher than for the nuclear plants (Centre d'Evaluation de la Protection dans le domaine Nucléaire, Fontenay-aux-Roses, F).

Another study paid attention to the asbestos industries in Great-Britain and France. The implicit value of the sanitary risk avoided was computed and compared to the figures related to nuclear industries (Centre d'Evaluation de la Protection dans le domaine Nucléaire, Fontenay-aux-Roses, F).

A comparative study of the impact on the environment of conventional and nuclear industries was started. The first efforts were limited to the methodological aspects of the study and to literature studies (Centre de Développement des Etudes et Applications en Hygiène et Sécurité, Avignon, F).

4.4. Conclusion

Neither the choice of an optimization method nor the value to be attributed to certain important parameters such as the cost of the man-sievert can be recommended a priori. The result of the optimization procedure constitutes only one factor among others to be taken into consideration by the decision-maker.

5. IN SUMMARY

The studies aimed at developing methods for evaluating the consequences of the irradiation of populations. After a complete analysis of the problems, they defined an overall methodology enabling the ICRP's latest recommendations to be met to a relatively satisfactory extent.

The methods of the evaluation of individual and collective doses, described in section 2, seem adequate in the majority of cases for solving the problem of the evaluation of the hazards arising from the normal operation of nuclear installations. Some additional research nevertheless appears to be essential in order to take account of the diversity of the characteristics of both the sources and receiving environments encountered in the Member States of the European Community. These methods should provide an important contribution to the compilation of total exposure data for the European population.

The studies carried out on methods for the evaluation of the radiological detriment to man, described in section 3, still provide a very fragmentory contribution to the problem of the establishment of a dose-effect relationship, in particular for low doses. The methods described in the fields of both epidemiology and animal experimentation have been applied to a number of specific cases and have underlined the need to extend the field of investigation towards a more realistic estimation of the hazard paying due attention to the great diversity of the exposure conditions and of the characteristics of the exposed populations. With regard to higher doses, the epidemiological studies relating to populations subjected to radiation treatments should be developed in view of improving the knowledge of the detriment in the event of an accidental situation. As far as low doses are concerned, further investigations will be encouraged towards possible combined effects of radiation and other concurrent environmental factors (tobacco, alcohol, socio-economic conditions and various forms of pollution).

In extending these studies, as described in section 4, the assessment of the cost of the radiological detriment should be supplemented by a new approach calling upon comparative studies of the levels of protection taken in different human activities, the implicit costs of avoided detrimental effects and the residual risks.

3. COORDINATION AND TRANSFER OF INFORMATION

The coordination of the activities of the contractants, the transfer of information between the contractants, within the European Community and to the outside world as well as the exploitation of the research datas were achieved, as shown in figure 2, by means of a variety of ad hoc meetings and specialized publications.

3.1. MEETINGS

Three different types of meetings were organized by the services of the Commission during the period 1976-1980 :

- Meetings of study groups, where scientists involved in the contract programme, independent experts and staff members of the Commission discuss specific subject areas of the programme

- Seminars or symposia organized or co-organized by the Commission around one or several themes directly related to contemporary problems in radiation protection

- Meetings of experts specifically designed, in accordance with Chapter III of the EURATOM Treaty, for the co-ordination and stimulation of efforts towards practical measures of radiation protection. The task of such working groups included, among others, the revision of Basic Safety Standards, the examination of Radioactive Effluent Discharge from nuclear power stations, the Assessment of Individual Dose and the Review of Reference Accidents.

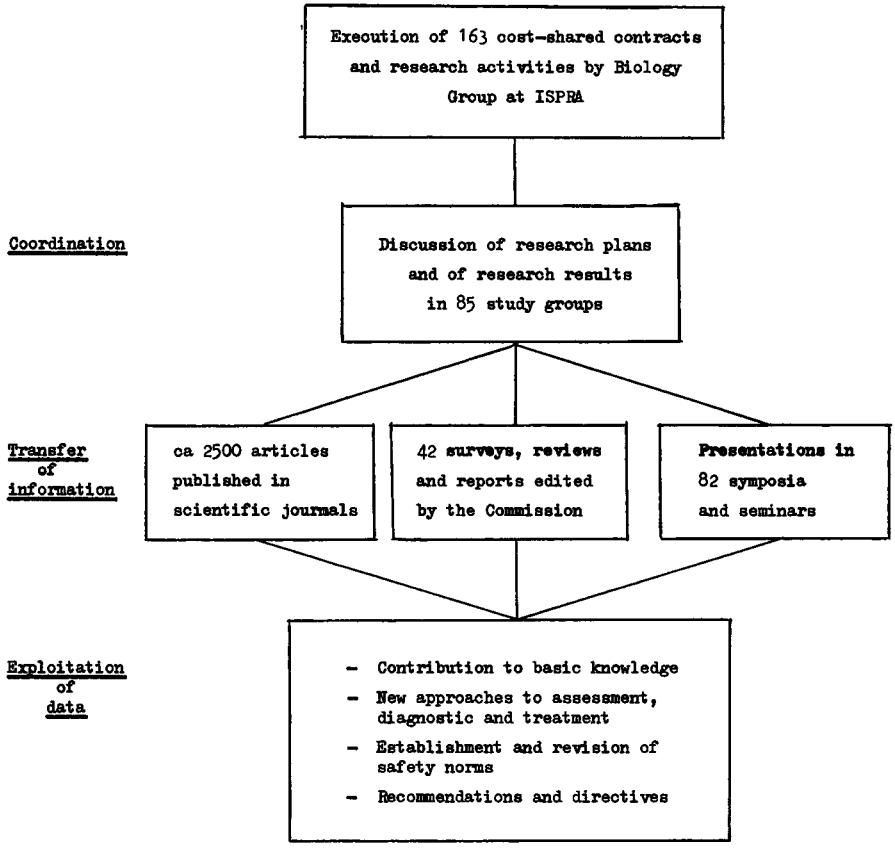
1)

The services of the Commission organized, from 1976 to 1980, a total of 85 study groups, 46 seminars and symposia and 36 meetings of experts. Details on each of these meetings are to be found in the progress reports issued annually by the Commission.

3.2. PUBLICATIONS

The results obtained during the 1976-1980 period have been published by the contractants in more than 2500 articles edited in scientific journals of international standing, references of which are given in the progress reports released by the Commission (Documents EUR 5711, EUR 5972, EUR 6263, EUR 6766, EUR 7169). In addition the Commission initiated surveys of detailed results of specific activities in the field of radiation protection and published them as monographs, proceedings and radiological protection data. A list of some of these publications is to be found in annex 3.

Figure 2. Coordination of research, transfer of information and exploitation of results during the period 1976-1980



ANNEXES

Annex 1 : List of contracting laboratories, classified by sectors, who participated to the Radiation Protection Programme during the period 1976-1980.

Annex 2 : Geographical distribution of contracts.

Annex 3 : Selection of publications issued on the initiative of the Commission during the period 1976-1980.

ANNEX 1

LIST OF CONTRACTING LABORATORIES, CLASSIFIED BY SECTORS, WHO PARTICIPATED TO THE RADIATION PROTECTION PROGRAMME DURING THE PERIOD 1976-1980

A. Radiation dosimetry and its interpretation

199-BIO N TNO, Rijswijk (Barendsen/Broerse)
176-BIO F Univ. Toulouse (Blanc)
211-BIO D GSF, Neuherberg (Jacobi/Burger)
170-BIO F Univ. Strasbourg (Rechenmann)
210-BIO D Univ. Homburg (Muth/Grillmaier)
164-BIO UK NRPB, Harwell (Dolphin)
188-BIO UK CEGB, Berkeley (Wheatley)
169-BIO UK NPL, Teddington (Lewis)
177-BIO F CEA, CEN Fontenay-aux-Roses (Parmentier)
215-BIO D KFA, Jülich (Feinendegen)
175-BIO I CNEN, CSN Casaccia (Silini)
208-BIO D Univ. Würzburg (Kellerer)
209-BIO D PTB, Braunschweig (Reich)
184-BIO UK Univ. Dundee (Watt)
178-BIO F CEA, CEN Grenoble (De Choudens)
246-BIO UK Univ. Aberdeen (Mallard)
229-BIO C CENDOS (Broerse et al.)
181-BIO C ICRU (Wyckoff)
185-BIA N ITAL, Wageningen (Ringoet)
167-BIO UK AERE, Harwell (Peirson)
201-BIO C EULEP (Duplan et al.)
103-PST I CNEN, Bologna (Busuoli)
106-PST D GSF, Neuherberg (Jacobi/Burger)
102-PST F Univ. Toulouse (Blanc)
098-PST UK AERE, Harwell (Peirson)
097-PST UK CEGB, Berkeley (Wheatley)
109-PST F CEA, CEN Fontenay-aux-Roses (Portal)
108-PST D PTB, Braunschweig (Wagner)
107-PST D KFA, Jülich (Heinzelmann)
111-PST UK NRPB, Harwell (White)
110-PST N TNO, Arnhem (Julius)

LIST OF CONTRACTING LABORATORIES, CLASSIFIED BY SECTORS, WHO PARTICIPATED TO THE RADIATION PROTECTION PROGRAMME DURING THE PERIOD 1976-1980

B. Behaviour and control of radionuclides in the environment

172-BIO I	CNEN, Fiascherino (Brondi)
219-BIO UK	MAFF, Lowestoft (Mitchell)
254-BIO F	Univ. Nantes/CEA La Hague (Pieri)
276-BIO D	Biol. Anstalt Helgoland (Hoppenheit)
280-BIO DK	Risó Nat. Labor., Roskilde (Aarkrog)
185-BIA N	ITAL, Wageningen (Sybenga)
258-BIO B	IHE, Bruxelles (Cantillon)
265-BIO B	Univ. Namur (Micha)
268-BIO N	Delta Instituut, Yerseke (Duursma)
235-BIO F	CEA, CEN Fontenay-aux-Roses (Bovard)
236-BIO B	CEN, Mol (Kirchmann)
237-BIO N	L.H., Wageningen (Van den Hoeck)
186-BIO UK	AERE, Harwell (Chamberlain)
231-BIO F	CEA, CEN Cadarache (Grauby)
260-BIO D	GSF, Hannover (Kühn)
269-BIO DK	Univ. Copenhagen (Nielsen)
255-BIO D	B.G.A., Berlin (Stieve)
187-BIO UK	AERE, Harwell (Chamberlain)
234-BIO B	Univ. Louvain (Myttenaere)
275-BIO B	Rijksuniversiteit, Gent (Deruytter)

LIST OF CONTRACTING LABORATORIES, CLASSIFIED BY SECTORS, WHO PARTICIPATED TO THE RADIATION PROTECTION PROGRAMME DURING THE PERIOD 1976-1980

C. Short-term somatic effects of ionizing radiation

220-BIO F	Cl. Bernard, Paris (Mathé).
221-BIO I	M. Negri, Milano (Garattini/Spreafico)
222-BIO D	Univ. Ulm (Fliedner/Heimpel)
198-BIO N	TNO, Rijswijk (Van Bekkum)
161-BIO B	Univ. Bruxelles (Tagnon/Stryckmans)
217-BIA D	GSF, München (Thierfelder)
191-BIO EIR	Univ. Dublin (Mullins/Greally)
159-BIO I	Univ. Napoli (Peschle)
173-BIO I	CNEN, CSN Casaccia (Doria)
263-BIO B	Univ. Brussel (Hamers)
230-BIO B	Univ. Bruxelles (Dumont)
250-BIO B	Univ. Louvain (Bazin)
257-BIO I	Univ. Firenze (Becciolini)
212-BIO D	Univ. Regensburg (Hüttermann)
213-BIO D	Univ. Giessen (Lohmann)
270-BIO D	HMI, Berlin (Schnabel)
214-BIO D	MPI, Mühleim (Schulte-Frohlinde/v.Sonntag)
226-BIO UK	Univ. Newcastle (Scholes/Garner)
158-BIO F	CEA, CEN Grenoble (Téoule)
271-BIO UK	Kennedy Institute, London (Harris)
227-BIO D	Primary effects (Köhnlein/Cramp et al.)
210-BIO D	Univ. Homburg (Muth/Grillmaier)
215-BIO D	KFA, Jülich (Feinendegen)
156-BIO B	Univ. Bruxelles (Brachet)
218-BIA D	GSF, Neuherberg (Gössner
266-BIO UK	Univ. Oxford (Wiernik/Hopewell)
252-BIO UK	Univ. London (Lindop)
249-BIO UK	MRC, Harwell (Vennart)
256-BIO DK	Univ. Copenhagen (Dané)

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LIST OF CONTRACTING LABORATORIES, CLASSIFIED BY SECTORS, WHO PARTICIPATED TO THE RADIATION PROTECTION PROGRAMME DURING THE PERIOD 1976-1980

D. Late somatic effects of ionizing radiation

201-BIO C	EULEP (Duplan et al.)
232-BIO B	CEN, Mol (Maisin
218-BIA D	GSF, Neuherberg (Gössner)
100-PST D	DKFZ, Heidelberg (Scheer)
266-BIO UK	Univ. Oxford (Wiernik/Hopewell)
264-BIO EIR	College of Technology, Dublin (Malone/Cullen)
179-BIO UK	NRPB, Harwell (Dolphin)
182-BIO UK	NRPB, Harwell (Dolphin)
105-PST UK	AERE, Harwell (Chamberlain)
174-BIO I	CNEN, CSN Casaccia (Clemente)
104-PST UK	AERE, Harwell (Morgan)
162-BIO I	CNEN, Bologna (Prodi)
252-BIO UK	Univ. London (Lindop)
243-BIO UK	PCL, London (Simmons)
249-BIO UK	MRC, Harwell (Vennart)
267-BIO UK	MRC, Harwell (Vennart)
278-BIO UK	UKAEA Winfrith, Dorchester (Ramsden)
277-BIO F	CEA, CEN Pierrelatte (Chalabreysse)
101-PST I	ENEL, Roma (Farulla)
242-BIO F	Fond. Bergonié, Bordeaux (Duplan)
241-BIO B	CEN, Mol (Maisin)
256-BIO DK	Univ. Copenhagen (Dané)
251-BIO DK	Univ. Copenhagen (Ebbesen)
253-BIO N	TNO, Rijswijk (Broerse/Barendsen)
207-BIO D	GSF, Neuherberg (Kriegel)
233-BIO B	CEN, Mol (Vanderborght)
151-BIO UK	MRC, London (Jones)
228-BIO I	Univ. Pisa (Donato)
216-BIO D	Univ. Erlangen (Pauly)
244-BIO D	GSF, Neuherberg (Drexler)
245-BIO UK	AERE, Harwell (Peirson)
199-BIO N	TNO, Rijswijk (Barendsen/Broerse)
215-BIO D	KFA, Jülich (Feinendegen)
208-BIO D	Univ. Würzburg (Kellerer)
248-BIO N	Univ. Leiden (van der Eb)
203-BIO DK	Finsen Institute, Copenhagen (Faber)
183-BIO EIR	College of Technology, Dublin (Taafe/Malone)
099-PSA F	CEA, CEN, Fontenay-aux-Roses (Uzzan)

LIST OF CONTRACTING LABORATORIES, CLASSIFIED BY SECTORS, WHO PARTICIPATED TO THE RADIATION PROTECTION PROGRAMME DURING THE PERIOD 1976-1980

E. Genetic effects of ionizing radiation

204-BIO DK	Univ. Aarhus (Marcker/Westergaard)
262-BIO DK	Univ. Aarhus (Celis)
194-BIO N	TNO/RU Leiden (Rörsch)
195-BIO N	TNO/RU Leiden (Sobels)
193-BIO N	TNO/RU Leiden (van der Eb)
248-BIO N	TNO/RU Leiden (van der Eb)
156-BIO B	Univ. Bruxelles (Brachet)
190-BIO EIR	Univ. Dublin (Winder)
189-BIO EIR	Univ. Galway (Houghton)
247-BIO EIR	Univ. Galway (Houghton)
196-BIO N	Univ. Rotterdam (Bootsma)
192-BIO N	Univ. Leiden (Simons)
200-BIO N	TNO, Rijswijk (Lohman)
166-BIO UK	MRC, Brighton (Bridges/Arlett)
163-BIO UK	Univ. Swansea (Parry)
154-BIO I	Univ. Pisa (Loprieno)
153-BIO I	Univ. Milano (Magni)
155-BIO F	Fond. Curie, Paris (Latarjet)
171-BIO UK	NRPB, Harwell (Dolphin)
167-BIO UK	AERE, Harwell (Peirson)
165-BIO I	Univ. Pavia (Fraccaro)
239-BIO F	INRA, Dijon (Dalebroux)
272-BIO F	INRA, Dijon (Dalebroux)
240-BIO F	Univ. Toulouse (Delpoux)
273-BIO F	Univ. Toulouse (Delpoux)
238-BIO B	CEN, Mol (Léonard)
274-BIO B	CEN, Mol (Léonard)
202-BIO DK	Carlsberg Lab.,Copenhagen (von Wettstein)
203-BIO DK	Finsen Institute, Copenhagen (Faber)
160-BIO I	Univ. Roma (Fasella/Whitehead)
168-BIO UK	PCL, London (Holt/Cohn)
183-BIO EIR	Techno., Dublin (Taaffe/Malone)
224-BIO B	Univ. Bruxelles (Radman)
152-BIO I	Univ. Pavia (Falaschi)
223-BIO F	CNRS, Gif-sur-Yvette (Devoret)
225-BIO F	CNRS, Gif-sur-Yvette (Anagnostopoulos)
150 BIO I	Univ. Roma (Olivieri)
206-BIO D	Univ. Göttingen (Hansmann)
205-BIO D	GSF, Frankfurt (Pohlit)
157-BIO B	Univ. Louvain (Goffeau)
261-BIO D	Univ. Giessen (Kiefer)
Biology Group,	CEC, Ispra (Devreux)
210-BIO D	Univ. Homburg (Muth/Grillmaier)
185-BIA N	ITAL, Wageningen (Ringoet)
232-BIO B	CEN, Mol (Maisin)
249-BIO UK	MRC, Harwell (Vennart)
101-PST I	ENEL, Roma (Farulla)
099-PSA F	CEA, CEN, Fontenay-aux-Roses (Uzzan)

LIST OF CONTRACTING LABORATORIES, CLASSIFIED BY SECTORS, WHO PARTICIPATED TO THE RADIATION PROTECTION PROGRAMME DURING THE PERIOD 1976-1980

F. Evaluation of radiation risks

099-PSA	F	CEA, CEN Fontenay-aux-Roses (Uzzan)
SC BC-1939	UK	Imperial College, London (Goddard)
SC 002	EIR	Trinity College, Dublin (Allwright)
SC 008	F	CEA, CEN Fontenay-aux-Roses (Lafuma)
SC 010	N	Univ. Leiden (Sankaranarayanan)
SC 016	I	Ist. Mario Negri, Milano (Tognoni)
SC 017	EIR	The Medical Research Board, Dublin (Dean)
SC 018	F	C.E.P.N., Fontenay-aux-Roses (Fagnani)
SC 019	F	Assoc. Willermé, Rennes (Massé)
SC 020	UK	St. George's Hospital, London (Bennett)
SC 021	F	C.C.P.N., Fontenay-aux-Roses (Fagnani)
SC 023	F	C.C.P.N., Fontenay-aux-Roses (Fagnani)
SC 024	F	C.C.P.N., Fontenay-aux-Roses (Fagnani)
SC 025	F	Hôpital Necker, Paris (Funck-Brentano)
SC 026	F	CEA, Fontenay-aux-Roses (Regnaud)
SC 027	F	CEA, Fontenay-aux-Roses (Caput)
SC 028	F	CEDHYS, Avignon (Chalabreysse)
SC 029	UK	Univ. Oxford (Gray)
180-BIO	C	ICRP (Lindell/Sowby)

ANNEX 2

GEOGRAPHICAL DISTRIBUTION OF CONTRACTS

BELGIQUE / BELGIE

Bruxelles
- Inst. d'Hygiène et d'Epidém.
- ULB
- VUB

Gent
- Univ.

Louvain
- UCL

Mol
- CEN

Namur
- Univ.

DANMARK

Aarhus
- Univ.

Copenhagen
- Carlsberg Laboratory
- Finsen Institute
- Univ.

Roskilde
- Risø Nat. Lab.

BUNDESREPUBLIK DEUTSCHLAND

Berlin
- Bundesgesundheitsamt
- FU *
- HMI

Braunschweig
- PTB

Erlangen
- Univ.

Frankfurt
- GSF

Giessen
- Univ.

Göttingen
- Univ.

Hamburg
- Biol. Anst.

Hannover
- GSF

Heidelberg
- DKFZ

Homburg/Saarbrücken
- Univ. *

Jülich
- KFA

Mülheim
- MPI

München
- GSF

Neuherberg
- GSF

Regensburg
- Univ.

Ulm
- Univ.

Würzburg
- Univ.

FRANCE

Bordeaux
- Fondation Bergonié

Cadarache
- CEA

Dijon
- INRA

Fontenay-aux-Roses
- CEA
- CEPN

Gif-sur-Yvette
- CNRS

Grenoble
- CEA

La Hague
- CEA **

Nantes
- Univ.

Orsay
- Others

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* Contract concluded with DKFZ
** Contract concluded with Univ. of Nantes

Paris
Association Cl. Bernard
Fondation Curie

Pierrelatte
CEA

Rennes
Ass. Villermé

Strasbourg
Univ.

Toulouse
Univ.

IRELAND

Dublin
Coll. of Technology
Univ.
Others

Galway
Univ.

ITALIA

Bologna
CNEN

Casaccia
CNEN

Fiascherino
CNEN

Firenze
Univ.

Ispra
CEC

Milano
Istituto Mario Negri

Napoli
Univ.

Pavia
Univ.

Pisa
Univ.

Roma
ENEL
Univ.

NEDERLAND

Arnhem
TNO

Leiden
Univ.
Others

Rijswijk
TNO

Rotterdam
Univ.

Wageningen
ITAL
Univ.

Yerseke
Delta

UNITED KINGDOM

Aberdeen
Univ.

Berkeley
CEGB

Brighton
MRC

Dorchester
UKAEA

Dundee
Univ.

Harwell
AERE
MRC
NRPB

London
Kennedy Inst.
MRC
PCL
Univ.

Lowestoft
MAFF

Newcastle
Univ.

Oxford
Univ.
Others

Swansea
Univ.

Teddington
NPL

GROUP CONTRACTS AND OTHERS

CENDOS
EULEP
ICRP
ICRU
Primary effects

ANNEX 3

SELECTION OF PUBLICATIONS ISSUED ON THE INITIATIVE OF THE COMMISSION DURING THE PERIOD 1976-1980

A. MONOGRAPHS AND PROCEEDINGS

- Problems posed by the growing use of consumer goods containing radioactive substances

  Proceedings of a seminar, Luxembourg, 13-14 November 1975

  EUR Report 5601, 1976, 161 pages

- Basic Physical data for Neutron Dosimetry

  Results of a workshop, Rijswijk, 19-21 May 1976, edited by J.J. BROERSE

  EUR Report 5629, 1976, 323 pages

- Radioactivité des eaux de la Meuse

  Compte-rendu d'un séminaire, Wepion, les 24 et 25 avril 1975

  Internal Doc. no. V-3559/1/75, 1976, 60 pages

- Bone marrow transplantation and other treatment after radiation injury

  H. BALNER

  Monograph, 1977, 83 pages

- First European Symposium on Rad-Equivalence

  Proceedings of a Seminar, Orsay, 24-26 May 1976

  EUR Report 5725, 1977, 265 pages

- First Information Seminar on the European Personal Dosimeter Intercomparison Programme (Photon-Intercomparisons 1974/75)

  21-23 June 1976, Berlin

  Internal Doc. no. 1623/77, 1977, 154 pages

- Information and Training on Radiation Protection for Trade Union Representatives from the nine Member States of the EC.

  Proceedings of the first and second seminar, Luxembourg, 7-8 October 1975 and 16-17 November 1976

  Internal Doc. no. 1957/77

- Effects of ionizing radiation on DNA; Physical, Chemical and Biological Aspects

  Monograph, 1978, 420 pages, 85 figures, edited by A. BERTINCHAMPS, J. HUTTERMANN, W. KOHNLEIN and R. TEOULE, Springer-Verlag Berlin

- Biological Effects of ^{224}Ra, Benefit and Risk of Therapeutic Application

  Proceedings of a Symposium, Neuherberg, 20-21 September 1976, edited by W.A. MULLER and H.G. EBERT

  1978, 236 pages, Martinus NIJHOFF Medical Division, The Hague

- Investigations into the emission of Carbon-14 compounds from nuclear facilities

  J. SCHWIBACH, H. RIEDEL and J. BRETSCHNEIDER

  Internal Doc. no. V-3062/78, 1978

- Third Symposium on Neutron Dosimetry in Biology and Medicine

  Neuherberg, 23-27 May 1977, edited by G. BURGER and H.G. EBERT

  EUR Report 5848, 1978, 950 pages

- Results of Environmental Radioactivity Measurements in the Member States of the European Community for Air - Deposition - Water - Milk 1975-1976, Luxembourg 1978

  EUR Report 5944, 1978, 328 pages

- A European Neutron Dosimetry Intercomparison Project (ENDIP) Results and Evaluation

  edited by J.J. BROERSE, G. BURGER and M. COPPOLA

  EUR Report 6004, 1978, 175 pages

- Sixth Symposium on Microdosimetry

  Brussels, 22-26 May 1978, edited by J. BOOZ and H.G. EBERT

  EUR Report 6064, 1978, 1261 pages

- Intermediate Energy Neutron Production; A Survey of Existing Techniques; A proposed Source and its Applications

  Final report of contract no. 135-74-7 BIO UK
  Central Electricity Generating Board, Berkeley Nuclear Laboratories, England

  A.J. MILL and J.R. HARVEY

  EUR Report 6107, 1978, 88 pages

- Radiation induced non-disjunction

  Proceedings of a Seminar, Brussels, 28-29 November 1978, edited by D. DE NETTANCOURT and K. SANKARANARAYANAN

  Special Issue of Mutation Research, 61, 1, 1979, 119 pages

- Methodology for evaluating the radiological consequences of radioactive effluents released in normal operations

  Internal Doc. V/3865/79, 1979

- Seminars on Radioprotection

  Proceedings of Seminars, Luxembourg, 10-11 October 1977 and 12-13 October 1978

  EUR Report 6264, 1979

- A Small Scale Neutron Dosimetry Intercomparison

  edited by J.J. BROERSE, J. ZOETELIEF, G. BURGER, H. SCHRAUBE and A. RECOURT

  EUR Report 6567, 1979, 38 pages

- Radiation Protection Optimization

  Proceedings of a Seminar, Luxembourg, 3-5 October 1979, edited by H. EBERT, H. ERISKAT, A. OUDIZ and G. UZZAN

  EUR Report 7001, 1979, 322 pages

- Chromosomal aspects of male sterility in mammals

  Proceedings of a workshop, Harwell, 24-26 October 1979

  in: J. Reprod. Fert., 60, 1980, pp 257-265

- Radiation repair in yeast

  Proceedings of a workshop, Louvain-la-Neuve, 10 September 1980

  Internal Doc., 1980, 16 pages

- Seminar on Radioactive releases and their dispersion in the atmosphere following a hypothetical reactor accident

  Proceedings of a Seminar in Risø, 22-25 April 1980

  CEC Report V/411, 1980, 1118 pages

- Irradiation and thyroid disease : dosimetric, clinical and carcinogenic aspects

  J.E. DUMONT, J.F. MALONE and A.J. VAN HERLE

  EUR Report 6713, 1980, 254 pages

- Ion chambers for neutron dosimetry

  edited by J.J. BROERSE

  EUR Report 6782, 1980, 351 pages

- Development and Testing of the Tandem Dose Equivalent Rate Meter for Beta and Photon Radiation to be used in Radiation Protection

  J. BOEHM and K. HOHLFELD

  EUR Report 6834, 1980

- A critical review of nuclear accident dosimeters

  B. MAJBORN

  EUR Report 6838, 1980

- Techniques for identifying transuranic speciation in aquatic environments

  Proceedings of a Technical Committee Meeting, Ispra, 24-28 March 1980

  IAEA, STI/PUB/613, 1981, 290 pages

- Radiation Protection Optimization : Present experience and methods

  Proceedings of a Seminar, Luxembourg, 3-5 October 1979

  EUR Report 7001, 1980, 322 pages

- 7th Symposium on Microdosimetry

  Proceedings, Oxford, 8-12 September 1980, edited by J. BOOZ, H.G. EBERT and H.D. HARTFIELD

  EUR Report 7147, 1981, 1588 pages

- European Seminar on Radiation Protection Quantities for External Exposure

  Proceedings, Braunschweig, 13-15 October 1980, edited by G. BURGER, H.G. EBERT, D. HARDER, R. KRAMER and S. WAGNER

  EUR Report 7101, 1981, 260 pages

- Bone and Bone-seeking Radionuclides : Physiology, Dosimetry and Effects

  Proceedings of a Symposium, Rotterdam, 29 August 1980, edited by V. WOLF

  EUR Report 7168, 1981, 153 pages

B. RADIOLOGICAL PROTECTION DATA

- Results of environmental radioactivity measurements in the Member States of the European Community for air - deposition - water 1973-1974, milk - 1972-1973-1974

  EUR Report 5630, 1977, 255 pages

- Review of existing information on external radiation from natural radioactivity in Europe

  Internal Doc. no. V-4024/77, 1977, 109 pages

- Results of environmental radioactivity measurements in the Member States of the European Community for air - deposition - water - milk

  EUR Report 6212, 1978, 290 pages

- Results of environmental radioactivity measurements in the Member States of the European Community for air - deposition - water - milk

  EUR Report 6620, 1980

C. OTHER PUBLICATIONS

- Catalogue of Contracts on the Radiation Protection Programme

  Containing information on the scientific content of the projects which make up the contract programmes, and on their administrative features such as contractor, duration, budget, etc.. The aim pursued through its publication is to convey a better transparency to the Commission's programme, and to serve as an aid for its management.

  For the convenience of the reader, contracts in the main part of the catalogue are systematically assigned to six major sections i.e. dosimetry, radioactive contamination of the environment, genetic effects, short-term and long-term somatic effects of ionizing radiation and evaluation of the radiation risk. In some cases where a contract is composed of several projects belonging to different sections, it is categorized according to its main research area. Therefore, a "list of research subjects" is given in the appendix where the relation between contracts and detailed subjects of the programme is clearly indicated. Furthermore, tables are added with details e.g. about geographical distribution of localities where research

is performed, and on the organizations and institutions to which the contractors belong. Finally a list of the scientific research group leaders is given. The catalogue refers to the situation in October 1977 (first edition) and to September 1979 (second edition).

Internal Doc. XII/919, 1979, 185 pages

- Radiation Protection Programme, 1980-1984
Research Priorities and Scientific Documentation (October 1979)

The Commission of the European Community has prepared a new multiannual research programme in the field of Biology - Health Protection concerning radiation protection and covering the period 1980-1984. The Council of Ministers agreed on that programme in December 1979.

The first part of this booklet contains the official proposal for the framework of the scientific programme as it was transmitted from the Commission to the Council of Ministers. It underlines the priorities derived from the present and foreseeable needs in radiation protection. In order to provide an overall view the research priorities have been grouped into six major sectors : radiation dosimetry and its interpretation, behaviour and control of radionuclides in the environment, short-term somatic, late somatic and genetic effects of ionizing radiation and evaluation of radiation risks.

The second part presents a documentation which is the outcome of the various ways in which the Commission has worked with the scientific community and assembled its views and opinions. As it is published it should give a detailed insight into the aims of the new Community Radiation Protection Programme and help interested institutions and scientists to prepare research projects and to improve joint planning and coordination.

Internal Doc. XII/1067, 1979, 345 pages