Pacific Northwest Laboratory Annual Report for 1984 to the DOE Office of Energy Research

**Part 4 Physical Sciences
February 1985**

**Prepared for the U.S. Department of Energy
under Contract DE-AC06-76RLO 1830**

**Pacific Northwest Laboratory
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J. M. Nielsen and Staff Members
of Pacific Northwest Laboratory

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Pacific Northwest Laboratory
Richland, Washington 99352

PREFACE

This 1984 annual report from Pacific Northwest Laboratory (PNL) to the Department of Energy (DOE) describes research in environment, health, and safety conducted during fiscal year 1984. The report again consists of five parts, each in a separate volume.

The five parts of the report are oriented to particular segments of our program. Parts 1 to 4 report on research performed for the DOE Office of Health and Environmental Research in the Office of Energy Research. Part 5 reports progress on all research performed for the Assistant Secretary for Policy, Safety, and Environment. In some instances, the volumes report on research funded by other DOE components or by other governmental entities under interagency agreements. Each part consists of project reports authored by scientists from several PNL research departments, reflecting the multidisciplinary nature of the research effort.

The parts of the 1984 Annual Report are:

Part 1: Biomedical Sciences Program Manager - J. F. Park	D. L. Felton, Report Coordinator and Editor
Part 2: Environmental Sciences Program Manager - B. E. Vaughan	B. E. Vaughan, Report Coordinator C. M. Novich, Editor
Part 3: Atmospheric Sciences Program Manager - C. E. Elderkin	N. S. Laulainen, Report Coordinator E. L. Owczarski, Editor
Part 4: Physical Sciences Program Manager - J. M. Nielsen	R. M. Garcia, Report Coordinator J. E. Danko, Editor
Part 5: Overview and Assessment Program Manager - W. A. Glass	R. W. Baalman, Report Coordinator and Editor

Activities of the scientists whose work is described in this annual report are broader in scope than the articles indicate. PNL staff have responded to numerous requests from DOE during the year for planning, for service on various task groups, and for special assistance.

Credit for this annual report goes to many scientists who performed the research and wrote the individual project reports, to the program managers who directed the research and coordinated the technical progress reports, to the editors who edited the individual project reports and assembled the five parts, and to Ray Baalman, editor in chief, who directed the total effort.

W. J. Bair, Manager
S. Marks, Associate Manager
Environment, Health and Safety
Research Program

Previous reports in this series:

Annual Report for

1951	W-25021, HW-25709
1952	HW-27814, HW-28636
1953	HW-30437, HW-30464
1954	HW-30306, HW-33128, HW-35905, HW-35917
1955	HW-39558, HW-41315, HW-41500
1956	HW-47500
1957	HW-53500
1958	HW-59500
1959	HW-63824, HW-65500
1960	HW-69500, HW-70050
1961	HW-72500, HW-73337
1962	HW-76000, HW-77609
1963	HW-80500, HW-81746
1964	BNWL-122
1965	BNWL-280; BNWL-235, Vol. 1-4; BNWL-361
1966	BNWL-480, Vol. 1; BNWL-481, Vol. 2, Pt. 1-4
1967	BNWL-714, Vol. 1; BNWL-715, Vol. 2, Pt. 1-4
1968	BNWL-1050, Vol. 1, Pt. 1-2; BNWL-1051, Vol. 2, Pt. 1-3
1969	BNWL-1306, Vol. 1, Pt. 1-2; BNWL-1307, Vol. 2, Pt. 1-3
1970	BNWL-1550, Vol. 1, Pt. 1-2; BNWL-1551, Vol. 2, Pt. 1-2
1971	BNWL-1650, Vol. 1, Pt. 1-2; BNWL-1651, Vol. 2, Pt. 1-2
1972	BNWL-1750, Vol. 1, Pt. 1-2; BNWL-1751, Vol. 2, Pt. 1-2
1973	BNWL-1850, Pt. 1-4
1974	BNWL-1950, Pt. 1-4
1975	BNWL-2000, Pt. 1-4
1976	BNWL-2100, Pt. 1-5
1977	PNL-2500, Pt. 1-5
1978	PNL-2850, Pt. 1-5
1979	PNL-3300, Pt. 1-5
1980	PNL-3700, Pt. 1-5
1981	PNL-4100, Pt. 1-5
1982	PNL-4600, Pt. 1-5
1983	PNL-5000, Pt. 1-5

FOREWORD

Part 4 of the Pacific Northwest Laboratory Annual Report for 1984 to the DOE Office of Energy Research includes those programs funded under the title "Physical and Technological Research." The Field Task Program Studies reports in this document are grouped under the subheadings and each section is introduced by a divider page that indicates the Field Task Agreement reported in that section. These reports only briefly indicate progress made during 1984. The reader should contact the principal investigators named or examine the publications cited for more details.

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Analytical Studies

• Chemical Basis for the Biological Response to Complex Organic Mixtures

The major focus of the analytical chemistry component in the complex mixtures program has been to identify biologically active constituents in materials related to coal conversion. Such studies at Pacific Northwest Laboratory (PNL) have also resulted in the identification of ways to reduce the biological activity of certain process materials. The more basic aspects of this research are funded by the Office of Health and Environmental Research; aspects relating to specific processes (e.g., integrated two-stage liquefaction) or modifications of these processes (e.g., heavy distillate recycle of SRC-II materials) are funded by the Office of Fossil Energy.

CHARACTERIZATION OF METABOLITES AND DNA ADDUCTS ARISING FROM DIRECT COAL LIQUIDS EXPOSURE

R. B. Lucke, B. W. Wilson and D. L. Springer

An area of increasing interest in the past year has been the metabolites formed from coal liquid chemical fractions and from pure compounds representative of those found in coal liquids. Separation of metabolic products formed *in vitro* using rat liver S-9 and *in vivo* using mouse skin has been developed. The further reaction of these metabolites with DNA to form adducts has also been investigated with the ultimate goal of isolating and identifying the coal liquid metabolite/DNA adduct. Such data will help to identify directly those specific compounds metabolized by the organism in such a manner as to ultimately bind to cellular DNA and thereby, assumedly, to initiate eventual development of tumor growth.

Figure 1 shows two chromatograms of a putatively adducted product of the reaction of benzo(a)pyrene (BaP) with radiolabelled guanine, a base found in DNA. Note the correlation in elution times for the radio-counting peaks indicating the presence of guanine and for the fluorescence peaks indicating the presence of a polynuclear aromatic hydrocarbon material such as BaP.

The analytical chemistry component of these studies is in its initial phases, and will continue to be developed in FY 1985. High performance mass spectral techniques that have recently become available, including chemical ionization desorption and fast atom bombardment, are slated to be used in these investigations.

FIGURE 1. Separation and Identification of DNA Adducts in Complex Mixtures.

DETERMINATION OF CHEMICAL PROPERTIES AND TOXICOLOGIC ACTIVITY OF HYDROAROMATIC SPECIES IN COAL LIQUEFACTION PRODUCTS

D. W. Later

Coal liquefaction products are primarily composed of polycyclic aromatic hydrocarbons (PAH) and their nitrogen, oxygen and sulfur derivative species. When subjected to catalytic hydrogenation conditions during liquefaction, PAH compounds lose aromaticity as hydrogen is incorporated into their molecular structure. Catalytic hydrogenation is currently being used as an integral process stage in contemporary, multiple-stage direct coal liquefaction facilities. Catalytic hydrogenation is used principally because it increases conversion efficiencies and H/C ratios and reduces levels of biological activity in laboratory assay systems. Hydroaromatic compounds are present at significant concentration levels in catalytically hydro-treated coal liquefaction materials. Analytical methods for the qualitative and quantitative determination of the hydroaromatic compounds, as well as understanding the impacts of catalytic hydrogenation on the biological activity of PAH, have therefore been of increased interest.

Both nonintegrated and integrated two-stage liquefaction samples investigated were materials from the distillation unit of the catalytic hydrotreater stage. For the most part hydroaromatic reference compounds used in these investigations were synthesized by catalytic hydrogenations of parent PAH in a batch autoclave.

The hydroaromatic compounds in the coal liquefaction materials were isolated into a discrete chemical fraction by adsorption/complexation chromatography. Briefly, the complex coal liquid is separated into aliphatic hydrocarbons, hydroaromatic compounds, and PAH class fractions on a gravity-flow alumina adsorption column doped with picric acid. The fully aromatic PAHs are retained the longest due to formation of strong picric complexes with the pi cloud of these compounds, while the hydro-substituted PAH, which form weaker picrates, are eluted earlier with less polar solvents.

Mass spectrometry, gas chromatography-mass spectrometry and high pressure liquid chro-

matography with diode array UV detection were used to determine the presence and structure of hydroaromatics in the fractions. In initiation/promotion assays, the picric acid fractions (PA₁ through PA₄) showed a wide differential in their activity, with their potency corresponding to increasing aromaticity, as would be expected. Thus, the mainly aliphatic fraction PA₁ was essentially no more active than the solvent control. Fraction PA₂ contained mainly tetrahydro, hexahydro and octahydro compounds and was slightly more active than fraction PA₁. The PA₃ isolate contained mainly dihydro compounds with some PAH having 3 rings or less and was more active than PA₂ or PA₁, but less active than fraction PA₄, which was composed mainly of aromatics having 4 or more rings.

These data indicate that hydroaromatic compounds are, as a general rule, less tumorigenic than their fully aromatic counterparts, and that the loss of tumorigenicity is related to decreasing aromaticity and increasing saturation or hydroaromaticity.

CHEMICAL ANALYSIS OF COAL-DERIVED MATERIALS IN COMMERCIAL USE

C. W. Wright, D. W. Later and B. W. Wilson

Extensive chemical class separations and chemical analyses were carried out on coal-tar-based topical agents (including shampoo, bath emulsion and pharmaceutical stock coal tar solutions in alcohol) used in symptomatic treatment of certain skin disorders. The chemical and toxicological properties of these materials were of interest because they have been used for several decades and yet there is no statistically significant indication of increased cancer risk in the exposed population.

Results of these studies showed that, in general, there was little difference chemically or toxicologically between the coal tar fraction that was extracted from these preparations and from a National Bureau of Standards (NBS) standard coal tar. All samples tested showed initiation activity in the initiation/promotion assay.

In microbial mutagenicity assays with Salmonella typhimurium TA98 each of the extracts or samples showed activity except for

a bath emulsion prepared with irradiated coal tar. It was assumed that ionizing radiation may have destroyed the amino-polycyclic aromatic hydrocarbons (APAH) that are known to give rise to mutagenic activity in this assay. Chemically, the materials were very similar with slightly lower phenol content due to extraction losses in those which required extraction from detergent. PAH carcinogens, such as methylchrysenes and benzo(a)pyrene, were present in all samples tested.

Possible explanations for the failure to detect increased cancer risk among populations exposed to these materials include the relatively short duration of each exposure event (these materials are often applied, then washed off the skin or scalp), and increased tolerance to chemical carcinogens by those suffering from certain types of skin disorders.

CHEMICAL CHARACTERIZATION OF MATERIALS FROM A CLOSE-COUPLED CATALYTIC-CATALYTIC TWO-STAGE COAL LIQUEFACTION PROCESS

B. W. Wilson and D. W. Later

Close-coupled two-stage liquefaction (CCTSL) is a coal conversion process in which both reactor stages contain a catalyst. No distillation or solids separation is carried out between stages, however, distillation and filtration are used to separate the final product material from the process stream leaving the second reactor. An objective of this process approach is to take maximum advantage of catalytically promoted reactions in converting coal.

Materials from this process, including tetrahydrofuran (THF) extracts of first and second stage reactor products, were assayed for chemical composition and mutagenic activity. Samples of the above materials were collected during a parametric run to ascertain process operability at reactor temperatures ranging between approximately 650° and 800°F; sample sets taken at three different temperatures were analyzed. The data were then used to compare these materials to analogous streams from other single- and two-stage technologies.

Mutational assays using the standard plate incorporation version of the histidine rever-

sion assay with *Salmonella typhimurium* TA98 showed that the mutagenic activity of the crude extracts was relatively low (in general, around 1 revertant per microgram or less on a dose response measure). Chemical fractionation of the materials followed by subsequent assays confirmed that most of the mutagenic activity was due to the nitrogen-containing polycyclic aromatic hydrocarbon constituents. Microbial mutagenicity arising from the presence of amino-PAH as a subfraction of the nitrogen-containing polycyclic aromatic compounds (NPAC) components in coal liquids is a characteristic common to those direct liquefaction process streams with boiling points above 650°F that have been studied to date.

Chemical analyses of the CCTSL materials utilizing liquid and high resolution gas chromatography, mass spectrometry and nuclear magnetic resonance spectroscopy (NMR) showed them to have high aliphatic and hydroaromatic content relative to single-stage and other two-stage processes. Aliphatic hydrocarbon (AH) fraction weights (including AH and some alkyl benzenes and cyclohexane compounds) were as high as 69% for the CCTSL second-stage product. This can be compared to single-stage materials for which an AH fraction weight of around 10% to 20% is common and to other two-stage processes that seldom exceed an AH fraction weight of 35% to 40%. Thus the CCTSL material may be characterized as "petroleum-like" relative to analogous materials from other direct coal liquefaction processes studied thus far.

ANALYSIS OF COAL AND COAL LIQUID COMBUSTION PRODUCTS

E. K. Chess, B. W. Wilson and D. W. Later

A limited effort has been made in the comparative chemical and toxicologic analysis of combustion products from coal and coal-derived liquid fuels. Studies on the controlled combustion of coal liquid fuels in electrical utility combustors have been published and show that there are few differences between the emission characteristics of petroleum-derived fuel oils tested and those of their coal-derived counterparts. However, no data are currently available on the relative chemical composition and toxicologic activity of the products from uncontrolled

combustion of these two types of materials such as would be encountered in an accident scenario involving tank cars or tank farm fires.

We have undertaken an analysis of the products of the open air combustion of petroleum- and coal-derived liquid fuels. Initial results indicate that much of the material extracted from the combustion particulate is chemically unaltered relative to that in the initial fuel. Hence, compounds such as amino-polycyclic aromatic hydrocarbons (APAH), as well as certain carcinogenic PAH, appear to simply volatilize and then recondense on carbon-based particulates formed during combustion. The failure of open flames to effect more complete combustion leads to marked differences in the chemical constituency of those petroleum-derived fuels tested as compared to the coal liquids. The coal-derived particulate extracts were slightly more mutagenic in their nitrogen-rich fractions than were the petroleum-derived extracts. These differences appear to be substantially greater than the differences noted for these two types of materials in recent utility combustion tests.

In collaboration with the Laboratory for Environmental and Health Research (LEHR) at the University of California at Davis, we have also compared the chemical composition and toxicology of coal combustion fly ash from conventional pulverized coal combustion (PCC) to that from newer fluidized bed combustion (FBC) technologies. In general, FBC-generated fly ash contained less extractable hydrocarbon and such extracts from FBC were less active in the histidine reversion assay for mutagenicity than were analogous extracts from PCC-derived fly ash. The mutagens from the PCC materials were more likely to contain nitrogen in their elemental composition, with nitro-PAH compounds making an important contribution to the overall mutagenic activity. Mutagens found in the active fractions of the FBC fly ash often contained oxygen as their only heteroatom. These studies indicated that newer FBC technologies are no more likely to give rise to adverse health effects than are the PCC technologies currently in use.

Measurement
and
Dosimetry

Investment

and

Development

• Supercritical Fluid Analytical Methods

Supercritical fluids are providing the basis for new and improved methods across a range of analytical technologies. New methods are being developed to allow the detection and measurement of materials that are incompatible with conventional analytical methodologies. Characterization of process and effluent streams for synfuel plants requires instruments capable of detecting and measuring high molecular weight compounds, polar compounds, or other materials that are generally difficult to analyze. The purpose of this program is to develop and apply new supercritical fluid techniques for extraction, separation and analysis. These new technologies will be applied to previously intractable synfuel process materials and to complex mixtures resulting from their interaction with environmental and biological systems.

SUPERCritical FLUID CHROMATOGRAPHY AND MASS SPECTROMETRY

R. D. Smith, B. W. Wright, and H. R. Udseth

Chromatographic methods combined with mass spectrometry comprise a nearly ideal analytical approach for characterizing complex mixtures. At Pacific Northwest Laboratory (PNL) supercritical fluid methods are being developed for materials where conventional gas or liquid chromatographic methods and existing mass spectrometric methods are inadequate (see references following this article). The advantages of supercritical fluid chromatography (SFC) accrue from the nature of supercritical fluids. The solvating properties of supercritical fluid mobile phases approach those of liquid phases, yet solute diffusivity typically remains one to two orders of magnitude higher. These properties allow high separation efficiencies to be realized while exploiting the variable and often high solvating power of the supercritical fluid. Consequently, SFC has the capability of separating thermally labile and nonvolatile solutes (a procedure not possible with gas chromatography) and can do so with higher efficiencies than liquid chromatography.

The introduction of the total chromatographic effluent into the mass spectrometer can be accomplished through the direct fluid injection (DFI) interface developed at PNL (Smith and Udseth 1983a). The coupling of capillary SFC with mass spectrometry (SFC-MS) offers significant advantages over existing high performance liquid chromatography-MS combinations. Supercritical fluids also offer advantages for transport of thermally labile compounds to the ion source since heating is not required for volatilization. The DFI

process provides for transfer of solutes in the supercritical fluid to the gas phase, so that conventional ionization methods can be used, while the matrix effects and uncertainties associated with desorption from surfaces can be avoided.

Three major accomplishments in the last year related to capillary SFC-MS include:

1. Nonextractable deactivated, bonded, and crosslinked stationary phases for very small diameter fused silica capillary columns (25-50 μm diameter) have been developed. These columns are useful for many nonpolar or less polar fluids and provide more than 5000 plates per meter. Over 100,000 effective plates can be generated in less than one hour. This high efficiency is enhanced further by the pressure programming capability of capillary SFC-MS.
2. The development of new rapid pressure programming methods for capillary SFC-MS allows high speed separations with enhanced sensitivity for mass spectrometric analysis.
3. The development of a DFI interface for electron impact ionization now allows total flexibility in selection of ionization method for SFC-MS and the use of existing libraries of mass spectra.

The high resolution and fast separation methods are compared in Figure 1, which shows separations obtained for a coal tar extract on 1) a 15 m x 50 μm column and 2) a fast separation on a short 1.75 m x 50 μm column with a rapid pressure program rate of 50 bar/min. This work serves to demonstrate the

FIGURE 1. Comparison of a High Resolution Capillary SFC-MS Analysis (top) with a Fast SFC-MS (rapid pressure programmed) Separation of the Same Coal Tar Sample. Structures or molecular weight of major polycyclic aromatic hydrocarbons are indicated in the figure.

versatility of the capillary SFC-MS approach. These methods and other related analytical methods are being further developed to allow extension to more polar and nonvolatile materials.

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• Lasers in Analytical Chemistry

The unique properties of laser light permit it to be applied to analytical chemistry in a variety of ways. Pacific Northwest Laboratory (PNL) is developing laser-based methods for measuring low levels of toxic materials and environmentally hazardous substances. This work has resulted in a number of new techniques in various stages of development. Kinetic phosphorimetry, a method for rapidly and accurately measuring low concentrations of uranium, has been developed over the past two years and has been the subject of a technology transfer program this past year. As a result, two companies are now building and planning to market an instrument based on this new technique. More recently, significant developments have been made in the use of continuous wave double-resonance ionization to analyze for atomic species. The first isotopically selective resonance ionization mass spectrometry has been performed, and a new technique called laser-enhanced electron impact ionization has been developed. In addition, research has been initiated in the new area of laser analysis of directly injected supercritical fluids. This technique offers great promise for the analysis of low-volatility molecular species.

TECHNOLOGY TRANSFER OF KINETIC PHOSPHORIMETRY

T. J. Whitaker and B. A. Bushaw

Kinetic phosphorimetry, described in the 1982 annual report (Bushaw 1983), has been the subject of a PNL technology transfer program. This technique provides rapid, accurate analyses for low concentrations of uranium in aqueous solution. It has several applications including bioassays, field assays for prospecting, and environmental monitoring. A prototype instrument based on this technology was displayed at the "Twenty-ninth Annual Conference of Bioassay, Analytical and Environmental Chemistry" in October 1983. A technical presentation was given at this and at other professional meetings, and direct communication was established with several instrument manufacturers. As a result of this program, two commercial companies plan to market an instrument based on kinetic phosphorimetry.

REFERENCE

Bushaw, B. A. 1983. "Laser Excitation and Kinetic Phosphorimetry: Measurement of Uranium in Solution at the Parts-Per-Trillion Level with True Instrumental Correction for Quenching Effects." In *Physical Sciences. Part 4 of Pacific Northwest Laboratory Annual Report for 1982 to the DOE Office of Energy Research*, pp. 23-24. PNL-4600 PT4, Pacific Northwest Laboratory, Richland, Washington.

CONTINUOUS WAVE DOUBLE-RESONANCE IONIZATION AND LASER-ENHANCED ELECTRON IMPACT IONIZATION

T. J. Whitaker, B. D. Cannon, and B. A. Bushaw

Resonance ionization spectroscopy (RIS) is recognized as an extremely sensitive analytical technique, but practically all experiments to date have been performed with pulsed lasers. Continuous wave (cw) lasers offer the advantage of narrow bandwidths for isotopic selectivity and an improvement of 10^4 to 10^5 in duty cycle.

We are developing a technique that uses cw dye lasers to excite an atom to a high electronic state by sequential excitation through a resonant intermediate state or by a resonantly enhanced two-photon process. The excited atom is then ionized by a high-power cw infrared laser. Initial experiments have been performed on an effusive atomic beam of barium generated from an oven at temperatures up to 600°C. Counter-propagating dye laser beams (5 to 10 mW) and the beam from a cw Nd:YAG laser (up to 100 watts) intersect the atomic beam at right angles in the ionizing region of a quadrupole mass spectrometer. Figure 1 shows the resulting mass spectrum when the frequencies of the two dye lasers are tuned so that their sum is resonant with the $F=7/2$ hyperfine level of ^{137}Ba in the $6s7d\ ^3D_2$ state. The relative ion yield of ^{137}Ba to ^{138}Ba in the figure is about 130, or 800 times greater than the naturally occurring

FIGURE 1. Isotopically Selective Resonance Ionization Mass Spectrum of Barium.

value (0.16). This indicates that the isotopic selectivity of the process is at least a factor of 800. The sensitivity has not been optimized nor accurately measured in these initial experiments, but it is expected to rival or exceed the ultrasensitivity of pulsed laser methods.

An isotopically selective ionization method requiring only one laser and a conventional electron impact (EI) ionizer has also been developed. This technique involves using the EI source at low energy and tuning the laser to a transition between the ground state and an excited state. As the laser populates the upper state, an enhancement is observed in the ion signal; thus, the name laser-enhanced electron impact ionization (LE²I²). If the laser is chopped (or pulsed) and phase sensitive detection is used, this technique could

provide a simple method for nearly eliminating isobaric interferences and improving the abundance sensitivity in mass spectrometry.

LASER ANALYSIS OF DIRECTLY INJECTED SUPERCRITICAL FLUIDS

B. D. Cannon, H. R. Udseth, T. J. Whitaker, and R. D. Smith

This method of direct injection of supercritical fluids, described in the 1983 annual report (Smith, Wright and Udseth 1984), is being investigated as a source of vapor phase molecules that may be probed by laser-induced fluorescence or resonance ionization mass spectrometry. This will allow normally low-volatility compounds, such as polynuclear aromatic hydrocarbons, to be introduced into a vacuum system as intact, vapor-phase molecules which may be analyzed by sensitive laser techniques. An added benefit of the direct injection process is the internal cooling that occurs in the molecule, an effect that produces sharp spectral features, and thus, better selectivity in laser analysis. Equipment is currently being assembled for initial experiments on this promising new technique.

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Physical
Processes

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PHYSICAL PROCESSES IN RADIATION BIOLOGY

The Radiological Physics programs address the physical processes of radiation action on biological systems. Through integrated, multidisciplinary studies, the interaction of radiation with matter and the chemical and biological response of the absorbing media are examined. The resulting information is integrated into predictive models of biological response.

The program focuses on acquiring increased understanding of the physical, chemical, and biological mechanisms of radiation action to better understand dose-response relationships in terms of quantifiable characteristics of the radiation and absorbing media. Experimental studies into the fundamental physical properties of energy deposition, energy transport, and cellular response are conducted to provide a data base for developing and testing chemical and biophysical models. Emphasis is on correlating radiation quality and energy transport with the formation of active chemical species, on understanding the mechanisms by which chemical agents interact at the cell level, and on developing models that correlate physical parameters of the radiation, chemical/biochemical interactions, and cellular repair phenomena with observed dose-response relationships.

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• Radiation Physics

Initial Interaction Processes

A fundamental knowledge of the mechanisms by which radiation interacts with matter is essential for understanding dose-response relationships in terms of quantifiable chemical and physical processes. Our study of the initial interaction processes in the absorption of energy from a radiation field has concentrated on the measurement and interpretation of absolute cross sections for the interaction of fast charged particles with atomic and molecular targets. Since ionization is the primary means of energy deposition by fast charged particles, we have emphasized measurements of total, differential, and partial ionization cross sections. Cross sections for the production of electrons, differential in ejected electron energy and emission angle, are required for detailed track structure information, whereas partial ionization cross sections provide information on the final states of the target atom molecule. Of particular interest is the determination of cross section systematics and interaction mechanisms that enable extrapolation of experimental results into regions where experiments are either impractical or unfeasible. During the past year, a major study of total ionization cross sections was published. This work is part of an ongoing collaboration with Prof. M. E. Rudd of the University of Nebraska. Theoretical studies of single differential cross sections for both electron and proton impact for atomic and molecular targets were completed and published. This work benefited from an active collaboration with Prof. S. T. Manson of Georgia State University. Considerable progress was made in the coincidence studies of interaction mechanisms leading to multiple ionization in ion-atom collisions. This work resulted in several papers, including two published in *Physical Review Letters*. A major milestone was also established in the study of ionization by structured ions. Data were obtained by coincidence techniques that enable separation of electron spectra resulting from target and projectile ionization.

DOUBLE DIFFERENTIAL IONIZATION CROSS SECTIONS

L. H. Toburen, R. D. DuBois, and
S. T. Manson*

The importance of charged particle track structure on the subsequent chemical and biological processes initiated by ionizing radiation is well recognized. An accurate representation of the detailed track structure relies on an accurate knowledge of the production and transport of secondary electrons. A major task of this program is to understand the mechanisms responsible for secondary electron production such that theoretical techniques can be used to reliably extrapolate cross sections to regions where data are unavailable. These studies involve measurements over as wide a range of experimental parameters as possible to obtain cross section systematics; these data can

then be compared to theoretical calculations to better understand the interaction process.

We have now compiled relatively extensive experimental cross sections for ionization of neon by protons. These data include proton energies from 0.3 to 4.2 MeV, accurate low energy electron data (time-of-flight derived) for proton energies from 0.3 to 1.5 MeV, low energy electron data for proton energies from 2 MeV to 4.2 MeV derived from oscillator strength measurements, data for emission angles from 15° to 130° (140° in special cases), and ejected electron energies to nearly 5 keV. These data are being compared to plane wave Born approximation calculations in which Hartree-Slater wave functions are used for initial discrete and final continuum wave functions. This calculation was previously described in a similar study of ionization of helium (Manson et al. 1975). In the present work we are taking a detailed look at the effects of additional electronic shells on the accuracy of atomic calculations. In general, the calculated and

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measured cross sections are in excellent agreement for neon for calculations that include the 1s, 2s, and 2p electronic levels. However, one rather interesting feature has lead us to further calculations to improve our understanding.

The theoretical results shown in Figure 1 show structure near the peak in the angular distribution. This structure is not confirmed in the experimental data. Our first interpretation of this structure was that perhaps the peak in the distribution of electrons ejected from the 2s and 2p shells occurred at different angles. However, a closer look showed that the 2p contribution itself contained structure. We are now exploring the possibility that the structure is an artifact of the wave functions used. Additional calculations will be performed using a full Hartree-Fock formulation. The divergence between theory and experiment for electrons ejected into small angles is expected due to the process of charge-transfer-to-the-continuum that is lacking in the calculation.

FIGURE 1. Emission of Electrons of 82 eV by 1.5 MeV Proton Impact on Neon. Solid and dashed curves are Born calculations using Hartree-Slater wave functions.

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THEORETICAL SINGLE DIFFERENTIAL CROSS SECTIONS FOR BARE IONS

J. H. Miller and W. E. Wilson

Semiempirical models that extend the data base of differential ionization cross sections have proved quite useful in applying these data to radiological, atmospheric and plasma physics. In recent years we have been particularly successful in developing models that are based on Bethe's theory of energy loss by fast charged particles. Since this model has been published elsewhere (Miller, Toburen and Manson 1983; Miller and Manson 1984; Wilson, Miller, Toburen and Manson 1984), we give only a brief description and present some new results for ionization of water vapor by electron impact.

The theory requires evaluation of coefficients in Bethe's asymptotic expansion of the first Born approximation to the inelastic scattering cross section of high velocity ions. These coefficients can be calculated from quantum mechanics; however this approach is laborious and of questionable accuracy for molecular targets. Recognizing that the desired coefficients are independent of projectile properties, we developed a semiempirical method to evaluate them that is based on measured optical oscillator strengths and proton impact ionization data at a single ion energy. We can then use the coefficients to predict the energy spectrum of secondary electrons ejected by any bare ion at any energy that is sufficiently large to make the Bethe theory valid.

Not only is this a very efficient use of differential ionization data, but also a very convenient way to incorporate these data into Monte Carlo track simulation computer codes. To facilitate the latter, we have developed

an algorithm consisting of two data tables and approximately 100 FORTRAN statements to calculate the single differential cross section for ionization of water vapor by protons at nonrelativistic energies that exceed 0.5 MeV. This algorithm is available upon request to any interested user (Wilson and Miller 1984).

Miller and Manson (1984) explicitly demonstrated that coefficients in the Bethe expansion that were deduced from optical and proton impact ionization data could be used to predict cross sections for ionization of rare-gas atoms by fast electrons. Figure 1 compares results obtained in the same way

with recent measurements (Bolorizadek 1984) of the spectrum of secondary electrons ejected from water vapor by 0.5 and 2 keV primary electrons. Several interesting discrepancies should be noted. First, the experimental results are significantly larger than our model predictions for secondary electron energies below 10 eV. Both model and experiment have large uncertainties in this energy range. Second, the experiment data tend to be larger than the model near the maximum secondary electron energy. This is particularly true for 2 keV primary electrons and is due in part to the fact that the experiment detects both scattered primaries and secondary electrons. Finally, the large discrepancy for ejection of 500 eV secondary electrons by 2 keV primary electrons is due to the Auger effect that is not included in the model.

FIGURE 1. Comparison of Theory (Solid Waves) and Experiment for the Spectrum of Secondary Electrons Ejected from a Water Molecule by 0.5 and 2 keV Primary Electrons.

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STRUCTURED ION IMPACT: DOUBLE DIFFERENTIAL CROSS SECTIONS

R. D. DuBois

For structured ion impact, the projectile arrives at the collision region with its own electron(s). Hence the electrons observed emanating from the collision region can arise from 1) target ionization or 2) projectile ionization. (Note that this is also the case for proton impact near the track end where the proton can pick up an electron from the medium and that electron can subsequently be stripped off).

Since the electrons arising from projectile ionization predominantly have very low energies in the projectile frame, they are strongly peaked in angle and energy in the laboratory frame. Hence, in some cases, it is possible to graphically separate them from the smooth underlying continuum of electrons due to target ionization. However, this separation is complicated because the underlying electron spectrum is produced by a projectile having a nuclear charge that is partially screened by its own electrons. This varying screening function is not known and can only be estimated.

To provide some information on this subject, we have initiated a new series of experiments in which the emitted electrons are observed in coincidence with another collision product. Using He^+ - Ar collisions as an initial test, we measured coincidences between emitted electrons and the direct beam (e^- , He^+) as well as between electrons and the stripped beam (e^- , He^{++}). These should correspond to target ionization and projectile ionization, respectively.

An example is shown in Figure 1. Although still very preliminary, the data imply that a smooth background drawn under the projectile ionization peak is incorrect. The target ionization is considerably smaller than this would imply. The projectile ionization data not only have a large cross section in the peak as expected, but also above and below the peak. This could possibly be an indication of simultaneous target ionization accompanying the projectile ionization. Further experimental and theoretical work is in progress to answer this question.

FIGURE 1. Relative Cross Sections for Electrons Associated with Projectile and Target Ionization in 1.6 MeV He^+ - Ar Collisions.

THEORETICAL CROSS SECTIONS FOR IONIZATION BY STRUCTURED IONS

J. H. Miller, L. H. Toburen and S. T. Manson*

Most of the energy deposited in tissue by ionizing radiation is delivered by structureless, charged particles (bare ions). At low velocity, positive ions may capture electrons from the medium to form structured ions. Since this occurs near the end of the particle range, the fraction of energy deposited in the charge-changing regions is small if the initial velocity is high. However, in some radiation fields secondary charge particles can be generated at velocities that favor charge exchange.

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The cross sections for ionization by structured ions are usually derived from bare ion data through the use of an effective charge. This approximation cannot explain the difference between the energy spectra of secondary electrons ejected by bare ions and that of structured ions (Toburen et al. 1981). Bound electrons on the projectile are very effective in screening interaction with targets in the medium when the impact parameter is large. Hence, glancing collisions become less important. Furthermore, ionization of the projectile produces secondary electrons with velocity nearly equal to that of the primary ion. Both of these effects tend to harden the secondary electron energy spectrum.

The Born approximation provides a conceptual framework for understanding the features of differential cross sections for ionization by structured ion, but ab initio calculations are only practical for simple systems (Manson and Toburen 1981). We have discovered that the characteristics of Bethe's theory for bare ions that make it amenable to semiempirical calculations can be carried over to structured ions. By including the form-factor of the orbital electron on the projectile in the integration over momentum transfer, the single differential cross section for target ionization can be expressed as

$$\frac{d\sigma}{dE} = \frac{4\pi a_0^2 (Z-N)^2}{T} \left[\frac{R^2}{E} \frac{df}{dE} \ln \left(\frac{4T}{R} \right) + B(E) + D \left(\frac{E}{T} \right) \right] \quad (1)$$

where a_0 is the Bohr radius (0.592×10^{-8} cm), R is the Rydberg energy (13.6 eV), $T = mv^2/2$ with m the electron mass and v the projectile velocity, $Z-N$ is the net charge on the projectile, E is the energy loss in the collision, df/dE is the optical oscillator strength of the target, and $O(E/T)$ denotes terms of order E/T .

Although Equation (1) has the same form as the Bethe theory for bare ions (Miller, Toburen and Manson 1983), it is not an effective charge approximation. The $B(E)$ coefficient in Equation (1) differs from that deduced for ionization of the target by bare ions in that for structured ions it contains

the dependence of projectile screening on energy loss. However, as was the case for bare ions, the $B(E)$ function in Equation (1) does not depend on the velocity of the projectile. Hence, single differential cross sections at one ion energy can be used to determine $B(E)$ for predicting cross sections at other ion energies. Work is currently in progress to implement this technique for ionization of argon by helium ions.

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TOTAL ION AND ELECTRON YIELDS

R. D. DuBois and M. E. Rudd*

In 1981, in collaboration with Prof. M. E. Rudd (University of Nebraska), we began an experimental investigation of total ion and electron production cross sections. The study emphasized absolute cross sections over a broad energy range for many atomic and molecular targets. Such cross sections are essential in evaluating our existing double differential cross sections and provide accurate normalizations for track structure calculations.

Initially the work concentrated on proton impact ionization. Cross sections from 5-4000 keV were measured and fitted to empirical equations. This greatly facilitates their incorporation into track structure computer codes. These data for ten atomic and

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molecular targets were published in Physical Review A in January 1984.

The H_2O data were missing from this initial study. These data have since been evaluated in the same manner and a manuscript has now been submitted to Physical Review A for publication.

In addition, this year we have turned our attention to He^+ impact. In this case, the data analysis is complicated by the large amount of charge transfer occurring in the experimental apparatus. Thus, the cross sections cannot be obtained with the same high degree of accuracy as was the case for proton impact. Results for He^+ impact were presented at the May meeting of the American Physical Society and are currently being incorporated into a full manuscript.

Our future plans are to continue this investigation for He^{+2} impact and, as the need arises, for selected systems.

MULTIPLE TARGET IONIZATION BY PROTON IMPACT

R. D. DuBois, L. H. Toburen, and
S. T. Manson*

Our experimental total and double differential cross section measurements provide no information about the final target ion charge state. It is generally assumed that single ionization dominates and that any multiple ionization occurs via the Auger channel.

However, in our measurements of multiple ionization due to proton impact, we found that approximately 60% of the electron production for high energy $H^+ - Kr$ collisions was the result of multiple ionization (DuBois, Toburen and Rudd 1984). Thus it is essential to incorporate multiple ionization into the theoretical picture of the collision; but to do so, we must determine what multiple ionization mechanisms are important. Hence, last year we determined cross sections for all relevant channels leading to double ionization of Ne by high energy proton impact (Manson, DuBois and Toburen 1983).

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We are now extending this analysis to other systems and charge states. We have also extended the analysis to lower incident ion energies where charge transfer becomes the dominant ionization mechanism. Our goal is to separate the measured multiple ionization into its charge transfer, inner shell and outer shell contributions. Preliminary results of this analysis were presented in an invited paper at an X84 international conference on X-Ray and Inner Shell Processes in Atoms, Molecules and Solids, held in Leipzig, East Germany, in August.

Results for double ionization of argon are shown in Figure 1. Here the total double ionization σ_2^T is broken into its component cross sections: double charge transfer σ_2^{1-1} , charge transfer plus ionization σ_2^{10} , direct double ionization σ_2^{11} and double ionization via the Auger channel σ_L^T .

FIGURE 1. Double Ionization of Argon by Proton Impact.

Such an analysis can be used to determine whether certain mechanisms should be incorporated into the theoretical picture or not. Exclusion of multiple ionization in a theoretical description can lead to serious errors as can be seen in Figure 2. Here we have measured the multiple target ionization for low energy H^+ impact on argon, but have separated the direct σ_n^{11} and single charge transfer σ_n^{10} channels through coincidence techniques (DuBois 1984). The important discovery was that the total electron production σ_- can be strongly influenced by the higher order charge transfer channel σ_2^{10} and is not dominantly due to direct single ionization of the target σ_1^{11} . Just how this affects the observed electron spectrum is not yet known.

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FIGURE 2. Cross Sections for Multiple Ionization of Argon Produced by Charge Transfer and Direct Ionization.

FIGURE 1. Graph showing the relationship between Energy and Y for various conditions. The curves are labeled A through Z.

It is an interesting fact that the results of the experiments described in this paper are in good agreement with the theoretical predictions of the theory of the photoelectric effect. The results of the experiments are shown in Figure 1, and the theoretical predictions are shown in Figure 2. The agreement between the experimental results and the theoretical predictions is very good, and this is a strong confirmation of the theory of the photoelectric effect.

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Track Structure

The initial spatial pattern of energy deposition by ionizing radiation plays a significant role in the subsequent evolution of biologically active chemical species. Radiochemical and radiobiological models of radiation action initiated by high linear energy transfer (LET) particles rely heavily on an accurate description of charged particle tracks. Our study of track structure includes both theoretical and experimental investigation of the spatial pattern of energy deposition. Incorporation of these data into models of energy transport in condensed phase clarifies the effects of the initial spatial patterns on evolving chemical yields. During the past year, a measurement of the radial distribution of ionization around high energy heavy ions has been continued at the Bevalac at Lawrence Berkeley Laboratory (LBL) in collaboration with Columbia University (H. Rossi) and LBL (J. Howard). Because of experimental limitations on determination of energy deposition in nanometer-sized target sites, we have also continued to develop Monte Carlo codes to calculate ionization and energy imparted in small sites. During the past year, we have concentrated on developing a theoretical treatment of the experimental data to enable extrapolation of data to higher ion energies. We have also continued investigation of systematics of energy loss spectra derived from the track structure codes. The detailed description of energy deposition provided by track structure codes has been used to derive the initial spatial pattern of chemical species along a charged particle track. This information, coupled with the reaction kinetics of liquid water, provides a direct means of calculating the yield of transient species in liquid water, beginning with interaction cross sections and following through to final yields. These data are compared with time-dependent yields measured for proton, deuteron, and alpha particle impact; reasonable agreement has been obtained.

MEASUREMENT OF ENERGY DEPOSITION NEAR HEAVY ION TRACKS

N. F. Metting, L. A. Braby, H. H. Rossi,*
P. J. Kliauga,* J. Howard,** M. Wong,**
W. Schimmerling,** and M. Rapkin***

In November of 1982 work was begun in collaboration with Columbia University and Lawrence Berkeley Laboratory to use microdosimetric methods to measure energy deposition of heavy ions produced at LBL's Bevalac Biomedical Facility. Details of the the experimental design have been given (Metting et al. 1984). Last year we reported preliminary results indicating that secondary charged particle equilibrium was probably obtained using this experimental setup, but that there seemed to be poor spatial resolution in the solid state position-sensitive detector (Metting et al. 1984).

Further analysis of the measurements taken in August 1983 shows that because of this electronic noise in the position-sensitive de-

tector, only the ^{56}Fe data yielded useful microdosimetric spectra. Figure 1 shows the probability density of lineal energy for primary ions crossing the site. The figure

FIGURE 1. The Frequency Distribution, or Probability Density, of Lineal Energy, y , Deposited by Primary Ions Crossing the Cylindrical Site. The data closely approximate the track length distribution inherent for the detector geometry, which is shown as a dashed line.

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shows a distribution of lineal energy $f(y)$, that closely simulates the track length distribution expected for a parallel radiation field crossing normal to a cylindrical detector volume (Kellerer 1984). The small number of events with y above 260 keV/ μ m is the result of energy loss straggling and proportional counter resolution.

When the energy depositions at all impact parameters are suitably combined, the microdosimetric distributions in lineal energy for an infinite parallel beam can be constructed. Figure 2 shows the curve $yf(y)$ versus the logarithm of y . When plotted this way, equal areas under the curve represent equal probabilities of those events occurring. Of interest is the fact that in irradiated tissue there is a greater probability that a cell will be hit by a low energy delta ray than by a primary ion event (see Figure 2). The frequency mean lineal energy, $\bar{y}_F$, for this distribution is 80.45 keV/ μ m.

Figure 3 shows the probability density of absorbed dose in y , multiplied by y , and plotted against the logarithm of y . When plotted in this way, equal areas under the curve represent equal contributions to the

FIGURE 2. The Probability Density of y for an Infinite Parallel Field. When plotted this way, $yf(y)$ versus $\log y$, equal areas under the curve represent equal probabilities of those events occurring.

FIGURE 3. The Probability Density of Absorbed Dose in y , for an Infinite Parallel Field. In this case, equal areas under the curve represent equal contributions to the dose delivered.

absorbed dose. It is evident from this figure that energy deposition from the primary ion accounts for most of the dose delivered.

The results of these experiments were reported in a paper "Microdosimetric Spectra of Heavy Ion Beams," presented at the annual Radiation Research Society meeting held in Orlando, Florida, in March 1984.

Physical refinements of the experimental design will continue so that this measurement can be made with the lower stopping power ions. The design has already been changed to allow a wider range of distances between the detectors and the solid wall in order to determine the precise relationship between primary ion velocity and secondary charged particle equilibrium.

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EFFECTS OF PHASE ON DIFFERENTIAL IONIZATION CROSS SECTIONS

J. H. Miller, W. E. Wilson and D. J. Brenner*

Our data base for understanding interactions of radiation with matter is obtained primarily from experiments in the gas phase; however, in radiological physics we are mostly concerned with energy deposition in a condensed medium. Hence, it is important to understand how intermolecular forces in condensed matter effect energy transfer and degradation. Phase effects can be divided into two categories (Inokuti 1982): 1) effects of phase on the transfer of energy from radiation to matter and 2) the phase dependence of energy degradation and formation of chemical species. The former, which is much better understood at present, is discussed in this section.

When high-velocity charged particles traverse a condensed medium, electronic polarization is induced that screens the interaction between the ion and the medium. In metals this can be described as collective oscillations of an electron gas in the field of the fixed ion cores (Bohm and Pines 1953). In a disordered insulator such as liquid water, collective excitations are considerably more localized and decay rapidly. For both metals and insulators, it is customary to discuss this effect in terms of a dielectric response function, $\epsilon(\vec{k}, \omega)$, that relates the electric field F of the moving point charge to the electrical displacement D in the medium by the equation

$$D(\vec{k}, \omega) = (\vec{k}, \omega) F(\vec{k}, \omega) \quad (1)$$

where $\vec{k}$ and ω are Fourier transform variables conjugate to the spatial and temporal coordinates of the field.

The dielectric function is a property of an extended medium analogous to the generalized

oscillator strength, $df(Q, E)/dE$, of an atom or molecule in that it describes the linear response of a system to small perturbations that involve transfer of energy $E = \hbar\omega$ and momentum $\vec{Q} = \hbar\vec{k}$, where $\hbar$ is Planck's constant divided by 2π . The precise relationship between the dielectric function and the generalized oscillator strength can be derived by comparing Bethe's sum rule on energy loss channels as applied to isolated molecules (Inokuti 1971) and extended media (Pines and Nozières 1966). This procedure leads to the result

$$\frac{R^2}{E} \frac{df(Q, E)}{dE} = \frac{1}{8\pi^2 n a_0^3} \text{Im} \left[\frac{-1}{\epsilon(\vec{k}, \omega)} \right] \quad (2)$$

where R is the Rydberg energy (13.6 eV), a_0 is the Bohr radius (0.529×10^{-8} cm), n is the number density of scatterers in the extended medium, and Im stands for "imaginary part."

Equation (2) is an important link between scattering theory in gas and condensed phases. In particular we may use it to investigate the effects of phase on our semi-empirical model for differential ionization cross sections (Miller, Toburen and Manson 1983). We have used an insulator model (Tung et al. 1976) with four ionization bands to analyze data on the dielectric response of liquid water (Heller et al. 1977). Applying Equation (2) in the $k \rightarrow 0$ limit, we used these results to obtain the $A(W)$ term in our model (Wilson et al. 1984). In Figure 1 the $A(W)$ coefficient for water in liquid and vapor phases is compared. We note a shift in the liquid spectrum relative to the vapor that favors production of more energetic secondary electrons in glancing collisions.

To predict single differential cross sections for liquid water we must also investigate the effects of phase on the $B(W)$ coefficient. Equation (2) makes this possible since the B coefficient can be expressed in terms of the generalized oscillator strength (Miller, Toburen and Manson 1983). However, at present there are no data on the k dependence of the dielectric response for liquid water. The insulator model used to fit the optical data on liquid water (Heller et al. 1977) also predicts the dielectric response for non-zero values of $\vec{k}$. The validity of this extension of the data on liquid water is being investigated.

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FIGURE 1. Comparison of the Coefficient of Glancing Collisions in the Spectrum of Secondary Electrons Produced in Water Vapor and Liquid Water by High-Velocity Ions.

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ION YIELDS IN LIQUID WATER

J. H. Miller, O. J. Brenner* and R. H. Ritchie**

Progress in modeling the phase dependence of differential ionization cross sections has provided some of the basic information needed to calculate ion yields in liquid water. However, since little is known about the physical mechanisms that determine the yield of chemical species in condensed matter, many assumptions must be made before we can connect the basic cross section data with picosecond yield measurements (Jonah and Miller 1977). Figure 1 summarizes our current model, which is similar to that reported by Turner et al. (1983).

Most ions are formed in glancing collisions with small momentum and energy transfer to the medium. In liquid water the final state of such collisions is expected to be a low-energy, quasi-free electron and a residual ion with a vacancy in one of the valence orbitals. Multiple ionization is neglected in the current model. The residual ion decays rapidly (10^{-14} seconds) to either the ground state of H_2O^+ or to a dissociative state. The branching ratios for this decay

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FIGURE 1. Mechanistic Model for Yield Calculations in Liquid Water.

are taken from gas-phase photoionization data (Tan et al. 1978).

The next step in our model of chemical species formation is electron solvation and proton transfer to produce OH radicals and H_3O^+ ions. The mechanism for production of solvated electrons is uncertain, but recent data (Wiesenfeld and Ippen 1980) suggest this occurs in less than 0.3 picoseconds and involves pre-existing deep traps rather than molecular reorientation. The initial separation of the solvated electron from its parent ion is a critical factor in determining the ion yield. We have estimated this distance in two ways: 1) by age diffusion theory (Roesch 1954) with electron stopping power derived from data on liquid water and 2) by detailed simulation of electron thermalization based on gas-phase data. Both methods give similar results. A recombination radius is derived from the bulk recombination

rate constant by assuming it is diffusion controlled. If the initial separation between solvated electron and parent ion is less than this radius, geminate recombination is assumed to occur.

The final step in ion yield calculations is to determine the kinetics of intratrack recombination. To allow for the effects of track structure, we have coupled our Monte Carlo track simulation program with the stochastic diffusion model of Clifford, Green and Pilling (1982). Preliminary results are encouraging but more code development is required before detailed comparison with the data of Jonah and Miller (1977) can be made. In particular, the effects of phase on differential ionization cross sections need to be incorporated into the track simulation programs and techniques for treating higher energy primary electrons need to be perfected.

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• Radiation Dosimetry

Dosimetry

The basic goal of the Radiation Dosimetry task is to explore the connections between the primary physical events produced by the interaction of radiation with matter and their subsequent biological consequences. Dosimetry concentrates on the physical aspects of the problem, emphasizing the use of fundamental physical data in deriving detailed dosimetric information. Special mathematical and experimental techniques are developed to investigate specialized dosimetry problems arising in radiobiological research and encountered in the environment. During the past year, the experience gained from these studies has been applied through national and international committees studying special dosimetry problems.

APPLICATION OF MICRODOSIMETRY TECHNIQUES IN HEALTH PHYSICS

L. A. Braby and N. F. Metting

In recent years tissue equivalent proportional counters (TEPC) and microdosimetric concepts have provided valuable insights into the nature of the interaction of various radiations with biological material. It is now becoming evident that these same techniques can be extended to improve measurements of mixed radiation fields for the purpose of radiation protection. A prototype instrument that we developed for NASA under a related services agreement has shown that it is possible to automate all of the necessary functions and to provide the required sensitivity in a compact portable instrument. Subsequent analysis of data collected with this instrument has shown that it produces dose equivalent and mean quality factor values in good agreement with calculated values for monoenergetic neutrons. Table 1 shows that the mean quality factor is within 0.5 in most cases and the dose equivalent is within 15%. Analysis of the spectra recorded by the instrument when it made these measurements shows that differences are partially due to fundamental differences in the quantities being compared. The calculated values are for neutron-produced secondaries only, while the instrument is designed to respond to the total dose, including that produced by incident photons. Thus the measured dose equivalent is expected to be slightly high for most irradiations and the quality factor slightly lower than the calculated value. The data also clearly show the effect of short-range secondaries in the case of 90 keV

TABLE 1. Quality Factors and Dose Equivalents Evaluated by the Instrument Compared to Standard Values

Neutron Energy (MeV)	Source	Q (max)	Q (measured)	H (measured)/H(max)
0.092	T(p,n)	7.2	5.5	1.29
0.20	T(p,n)	8.9	8.5	1.13
0.56	T(p,n)	11.0	10.5	1.06
0.90	T(p,n)	10.7	10.3	0.90
2.0	D(d,n)	9.3	8.7	0.84
4.1	D(d,n)	8.1	7.8	0.88
15.3	T(d,n)	6.3	6.3	0.96
2.35 spectrum	²⁵² Cf	8.6	7.4	1.34
4.2 spectrum	²³⁹ PuBe	8.1	7.4	1.05

neutrons. These protons do not cross the 2 μ m simulated site and are consequently assumed to have lower linear energy transfer (LET). This is one area of TEPC application that still requires significant improvement.

Three papers describing the potential applications of microdosimetry were prepared during 1984. "Evaluation of a Portable Microdosimetry System" was presented at the Workshop on Practical Implementation of Microdosimetric Counters in Radiation Protection and has been accepted for publication in *Radiation Protection Dosimetry*. "A Portable Microdosimetry System" was presented at the Fifth Symposium on Neutron Dosimetry. "A

Portable Dose Equivalent Meter Based on Microdosimetry" will be presented at the Eighth Conference on the Application of Accelerators.

POSITIVE ION IRRADIATION FACILITY

L. A. Braby

Many questions about the mechanisms of the response of cells to ionizing radiation can best be investigated using monoenergetic heavy charged particle beams. Questions of the role of different types of damage in the LET effect, for example, are being answered by comparing repair kinetics for damage induced by electrons with that produced by helium ions. However, as the models become more sophisticated, the differences between models can be detected only with more precise measurements, or by combining high- and low-LET irradiations in split-dose experiments. The design of our present cell irradiation beam line has limited us to irradiating cells in a partial vacuum. The minimum time for placing a group of dishes in the system and preparing them for irradiation has been about 20 minutes, much too long for damage interaction studies. Also, we needed to extend these studies to plateau-phase mammalian cells. However, there was no way to guarantee that there would not be an interaction between the radiation damage and the stress of evacuation. Thus, a new way to mount the dishes and bring the beam to the cells was required. We needed to be able to irradiate as many mammalian cells as possible, in air, through a thin mylar-film bottom of special dishes, and also to irradiate *Chlamydomonas* on agar in a partial vacuum with a quick turnaround time. Several means of irradiating cells in mylar-bottom dishes have been used at other laboratories. For example, at the RARAF facility, the dual ion experiments are done with the dish bottom serving as the beam exit window but the cells are in a partial vacuum to prevent breaking the window. In other experiments the dish is scanned across a rectangular window that is curved like a segment of a cylinder to reduce stress at the corners. This system involves a path in the gas at atmospheric pressure of as much as 1 cm between the exit window and the cell support, and a variable path length through the window. For our experiments these methods presented serious limitations. Scanning

the dish across the beam was not compatible with the high dose rates planned for mixed radiation studies. Also, the variation in path length through a sharply curved window presented a potential problem. We have chosen instead to use the dish bottom as the beam window and to irradiate the entire dish in a single exposure. This will require small dishes, but since we will be using plateau-phase cultures, there will be a reasonable number of cells.

A special, very fast pumping system will be installed at the end of the beam line. This system will make it possible to irradiate cells within two minutes of installing them in the irradiation chamber. In this way, the interaction of electron and ion-induced damage in *Chlamydomonas* can be studied with time between doses as short as 5 minutes. This should be adequate to study the interaction of damage that has a mean repair time of 25 minutes.

RE-EVALUATION OF THE HIROSHIMA-NAGASAKI RADIATION DOSES

W. C. Roesch

On November 8-9, 1983, the National Academy of Sciences Panel on Reassessment of A-Bomb Dosimetry and its Japanese counterpart held the Second U.S.-Japan Joint Workshop for Reassessment of Atomic Bomb Dosimetry at Hiroshima. The proceedings of that meeting have appeared, including my rapporteur report of one of the sessions (Roesch and Dake 1984). The Panel itself met on December 7, 1983, and on October 19, 1984. The Department of Energy Working Group on A-Bomb Dosimetry met on November 7, 1983, and on February 6-7 and June 6, 1984.

One of the problems that arose during these activities was to estimate the uncertainty in the measurements made of ^{32}P induced in sulfur in telephone-pole insulators at Hiroshima. I developed the necessary theory, a theory of ionization fluctuations, for the purpose. One of the key parameters in the result is no longer accessible to measurement, but we were able to approximate it by measurements made with equipment used in our studies in microdosimetry.

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BETA-PARTICLE DOSIMETRY

W. C. Roesch

The National Council on Radiation Protection chose the members for its Scientific Committee #80, Radiobiology of the Skin. They are F. J. Burns (New York University), P. D. Forbes (Temple University), T. F. Gesell (DOE, Idaho Falls), F. D. Malkinson (St. Lukes Hospital, Chicago), H. R. Withers (University of California, Los Angeles), and W. C. Roesch, Chairman (Pacific Northwest Laboratory). The committee met on April 24-25, 1984, to establish its program. First rough drafts of a report on radiobiology of the skin were delivered to the chairman by September 1. I consolidated and edited this material in time for the next meeting of the committee on November 15-16, 1984. I delivered one paper (Roesch 1984a) on the nature and work of this committee and another (Roesch 1984b) on a way of dealing with one of the principal problems the committee faces, i.e., properly averaging the dose in different parts of the skin.

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CALCULATIONS OF DOSE DISTRIBUTIONS

W. C. Roesch

The National Council on Radiation Protection's Scientific Committee #52 on Conceptual Basis of Calculations of Dose Distributions met March 30-31, 1984, and completed work on its report to the Council. The final draft is now in the hands of the committee members for proofing.

LOW-VOLTAGE NEUTRON GENERATORS

W. C. Roesch

The National Council on Radiation Protection's Scientific Committee #25 on Radiation Protection and Measurement for Low-Voltage Neutron Generators completed its work a few years ago. I was chairman of the group. Its final report, Radiation Protection and Measurement for Low-Voltage Neutron Generators, has been published.

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Modeling and Cellular Studies

The effects of ionizing radiation on living systems begin with the basic physical processes of energy deposition and develop through many stages of chemical reactions and biological responses. The modeling effort attempts to develop mathematical descriptions of the response of cells to radiation and to provide a systematic means of interpreting the biological response in terms of quantifiable physical parameters of the radiation field. Studying the kinetics of cell response as a function of dose, dose rate, and radiation quality provides a means of testing fundamental assumptions regarding the mechanisms of damage and repair.

Mathematical modeling and cellular studies complement each other. Modeling provides guidance in designing experiments capable of disproving the model, while the experiments themselves provide new input to the model. Based on previous experimental results, the model for the accumulation of damage in *Chlamydomonas reinhardtii* has been extended to include various multiple two-event combinations. Since conventional split-dose experiments at low linear energy transfer (LET) cannot discriminate between these models, they have been extended to include ion irradiations at LET up to 100 keV/ μm .

LINEAR ENERGY TRANSFER (LET) EFFECTS ON REPAIR RATE

L. A. Braby and J. M. Nelson

Studies of the repair rate for cells exposed to charged particles of different LET provide important information on the kinds of kinetic processes that should be considered in detailed mathematical models. In a preliminary study with *Chlamydomonas reinhardtii* (Braby and Jacobson 1984), we tentatively concluded that the repair rate was the same for 13 keV/ μm proton and 81 keV/ μm ^3He ion irradiation, thus suggesting that the same type of damage, repaired by the same process, was predominant in both cases. However, this conclusion was very tentative because of limited precision in the repair rate measurement. Two factors limited that precision: lack of temperature control and limited reliability of the accelerator ion source.

Since the repair rate in *C. reinhardtii* is known to be a strong function of temperature (Braby, Nelson and Roesch 1979), the lack of temperature control prevented use of repeated experiments to improve the statistics of the measurement. Since the cells are irradiated in an atmosphere of air and water vapor at about 1/15 of atmospheric pressure and are held in that atmosphere for up to two hours, we have provided temperature control at three critical points: a conditioning incubator to bring the dishes to the desired temperature,

the water used to humidify the gas flowing into the chamber, and the walls of the vacuum chamber and beam line. By controlling the beam line temperature, heat transfer by thermal radiation is eliminated. This temperature control equipment provided the opportunity to perform experiments at specified temperatures. Previous work with 1.5 MeV electrons gave a mean repair time of 40 minutes at 20°C, while the 3 MeV proton and 6 MeV ^3He ion data give 43 and 47 minutes, respectively. These values are within the expected errors that are only a few minutes for the electrons and protons, but increase to over ten minutes for the ^3He ions. This increased uncertainty results from the small amount of repairable damage produced by the helium irradiation. The maximum survival and the observed survival are nearly the same so there is a large uncertainty in the difference.

The temperature control also permitted us to start checking for the multiple repair processes observed in electron irradiations. Figure 1 shows data to 30°C, just above the point where fast repair is first observed for low LET radiations. There is a strong suggestion of a higher slope between 0 and 5 minutes, indicating the existence of the fast repair process. However, this cannot be quantitated because of limited data at longer times. The limited amount of data is due to an interaction between ion source components required for production of proton and helium

FIGURE 1. Split-Dose Survival Data from *C. reinhardi* Irradiated at 30°C Showing an Initial Rapid Repair in Addition to a Slower Component with a Mean Repair Time of 41 min.

beams. The dual plasmatron can produce H^+ ions for injection into the tandem quite efficiently, and will normally operate reliably for many days. However, He^+ cannot be made directly, but must be produced in a charge changing system using a Cs vapor oven. Unfortunately, it has proved to be impossible to prevent the cesium vapor from contaminating the insulators of the dual plasmatron and its lenses. This contamination has shortened the ion source running time to a few hours and has prevented completion of most of the planned experiments. To overcome this, a third ion source system specifically for He^+ ions is being installed on the tandem. We hope that this RF source will be free of cesium vapor problems since its focusing electrodes are more easily shielded. In any case, it will not contaminate the dual plasmatron and proton beams will again be reliable.

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IMPROVING THE PRECISION AND RANGE OF CELL SURVIVAL ASSAYS

L. A. Braby, J. M. Nelson, and M. K. Lien

Most of the biophysical models that we would like to evaluate predict nearly equal survival except at very high surviving fractions. Thus, to test these models, survival data must be unusually precise. This requires determining the actual number of cells at risk, counting large numbers of clones, or both. As a part of our continuing program to improve the efficiency of our experiments, we have automated the counting of clones in split-dose experiments. This allows us to count much larger numbers of clones than previously and reduces the man-hours required. We first evaluated a commercially available bacterial colony counter for this purpose, but it was not sufficiently accurate. Some computer-based systems have been described in the literature but these have required operator assistance to confirm the machine's decisions. We chose to assemble a fully automated system and to accept the small variations between the counts produced by this system and those produced by a well-trained individual. The system was also designed so that it could be expanded to include individual cell counting and potentially to evaluate growth curves (number of cells versus time) of individual clones.

The image to be analyzed is produced by a video camera viewing a little less than half of a 15 cm^2 tissue culture flask. The video camera is connected to a Grinnell image processing system with 512×512 pixel memory which is in turn interfaced to a VAX 750 computer. The digital information for the two pictures required to cover each dish is entered into a disk file along with the dish identification number. Two hundred dishes

are typically processed in a batch to avoid interfering with other computer use. In a little over one hour, the typical operator can enter the dish numbers and position the dishes for the resulting 400 pictures. The clone counting procedure is run as a batch job and is illustrated in the flow diagram, Figure 1. Since a predetermined threshold is used to distinguish cell areas from background areas, it is important that the contrast be as great as possible and that the background be uniform. Contrast is heightened by staining the cells with crystal violet in the usual way and using a 550 nm band-pass filter for the illumination. A radiometric background correction is used to eliminate small variations in illumination and camera sensitivity. To eliminate single cells and to simplify determination of the area of clones, all black pixels with less than 3 black neighbors (edges and corners) are eliminated. The area of each remaining black object is then determined. The computer scans rows in sequence until it encounters a black pixel. It then identifies and counts all adjacent black pixels making up that object and records the location and the total number of pixels in the object. After all of the black objects in the screen have been identified and their area determined, the number of objects with sufficient area to qualify as a surviving clone is written to a file. Additional software has been written to use this file of clone count data, plus a file of dilution data and electronic particle counter data to calculate surviving fractions and repair rates.

Automated counting has reduced the operator time needed to count the clones in a typical experiment with 600 assay dishes from about 130 hours to about 4 hours. This reduces the total time required to do the experiment to about one-quarter of the former time. The next obvious step is to provide direct entry

FIGURE 1. Automatic Clone Counting System.

of the data on the number of cells at risk. If this can be done by counting the cells as they enter the assay flask, data entry time will be reduced and survival data governed by binomial statistics will be provided, thus reducing uncertainties even further in high surviving fraction data.

● Radiation Biophysics

Experimental studies in cellular radiobiology are undertaken to provide comprehensive tests of theoretical models that relate biological phenomena with their initiating physical events. These studies are closely coordinated with the models being developed in the Radiation Dosimetry task, giving laboratory support and guidance to development of the theory. Studies involving synchronized mammalian cell cultures [Chinese hamster ovary (CHO) cells] and various irradiation parameters such as dose rate, dose fractionation, and radiation quality are designed and selected to provide optimum tests of the theory. To perform dose and dose-rate measurements at low doses, cells with constant radiosensitivity are required. To provide this consistency with mammalian cells, stationary-phase cultures must be used. The kinetics of stationary cell systems have been thoroughly evaluated. Repair of single-event and cumulative damage resulting from exposure of these and other cell systems to ionizing radiation is being investigated.

DOSE-RATE EVIDENCE FOR TWO KINDS OF RADIATION DAMAGE IN STATIONARY-PHASE MAMMALIAN CELLS

N. F. Metting, L. A. Braby, W. C. Roesch, and J. M. Nelson

Survival based on colony formation was measured for starved plateau-phase Chinese hamster ovary (CHO) cells exposed to 250 kV X-rays at dose rates of 0.0031, 0.025, 0.18, 0.31, and 1.00 Gy/min. A large dose-rate effect was demonstrated. Delayed-plating experiments and dose-response experiments following a conditioning dose, both using a dose rate of 1.00 Gy/min and delays of up to 48 h, were also used to investigate the alternative repair hypotheses. There is clearly more repair in a dose-rate experiment than is observed in both the delayed-plating and the conditioning dose measurements combined. Thus, we believe that at least two types of damage with distinct repair pathways are being observed. We have applied the Damage Accumulation Model (Braby and Roesch 1978) to separate two types of radiation damage and to estimate the repair rate for that type of damage which becomes lethal only through interaction with additional damage, i.e., sublethal damage. The mean time for repair of this sublethal damage is estimated to be 70 min for our CHO cells. Use of this analysis on other published dose-rate studies also yields results consistent with this interpretation of the repair mechanisms.

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SUBLETHAL DAMAGE IS NOT THE SAME AS POTENTIALLY LETHAL DAMAGE

J. M. Nelson, N. F. Metting, L. A. Braby, and W. C. Roesch

The response of cultured cells exposed to ionizing radiations has been interpreted by different researchers according to several different models. These models usually assume that the shape of the survival curve and the split-dose effect result either 1) from the accumulation and interaction of sublethal damage, or 2) from the saturation of a potentially lethal damage repair mechanism. Our Damage Accumulation Model assumes the existence of both single- and multiple-event damage, with exponential removal of the latter. This damage removal process corresponds to the repair of sublethal damage. Other investigators consider the shoulder on the survival curve, as well as related phenomena, to be a consequence of the same type of biochemical mechanism that leads to the delayed-plating effect, i.e., potentially lethal damage repair. The essential question

is, therefore, whether or not the damage removal processes observed in different types of experiments (designed specifically to observe the different types of repair) are the same. It is generally agreed that both sublethal (if it exists) and potentially lethal damage repair could affect the results of split-dose and dose-rate experiments, but only potentially lethal damage repair would affect delayed-plating results.

There are remarkable differences between the families of survival curves generated by delayed-plating and those of dose-rate experiments (Metting et al. 1984). The family of curves resulting from different dose rates shows both a reduction in the slope of the curve and a loss of the shoulder. In contrast, little more than a change in the shoulder is evident as a result of delayed plating. Albeit such a comparison is qualitative, it suggests the existence of more than one kind of damage removal process. To substantiate these findings and to quantitate the kinetics of the observed processes, we have studied the time-dependent removal of ionizing radiation damage in stationary-phase CHO cells using a variety of different irradiation schedules.

According to the Damage Accumulation Model, when split-dose survival data for a system with a single repair process are plotted as $\ln(Sm/S)$ on a log scale (Sm is the theoretical maximum survival that would result if the two doses were separated by an infinite time and complete repair were allowed to take place) against time between fractions, the data fall on a straight line. The mean repair time (τ) is the negative reciprocal of the slope of this line. If an additional repair process is present, the data can be mathematically separated in much the same way as they would be separated in the case of a mixture of radioisotopes having different half-lives. Survival data from split-dose experiments with starved plateau-phase CHO cells show two simultaneous damage removal processes. As seen in Figure 1, one of these processes has a characteristic time on the order of 60 min, the other, about 16 to 20 h. If both processes were removing the same type of damage, they would appear to have only a single, average repair rate, so we are forced to conclude that two distinct types of damage are present.

FIGURE 1. Split-Dose Survival Data for Starved Plateau-Phase CHO Cells Irradiated at 37°C. Two components of repair can be separated, demonstrating mean repair time of about 18 h and 1 h.

Delayed-plating experiments reflect only the removal of potentially lethal damage. As seen in Figure 2, delayed-plating techniques demonstrate only a single repair process having a characteristic time of about 18 h. We can either analyze the delayed-plating data in a way similar to that used for the split-dose data, or we can plot the fraction of damage remaining against the time interval between irradiation and subculturing, as seen in Figure 2. In either case, the characteristic time of the single process observed is on the order of 16 to 20 h.

We have recently attempted to compare the amount of damage produced in the presence and absence of oxygen that can be removed by potentially lethal and sublethal damage repair processes. Starved plateau-phase CHO cells were used because their kinetic status is well documented (Nelson, Todd and Metting 1984). Survival curves from cells irradiated

FIGURE 2. Delayed-Plating Data for Starved Plateau-Phase CHO Cells Irradiated at 37°C, Plotted as the Fraction of Damage Remaining Against Time. These data suggest a single process with a mean repair time of about 18 h.

under well-oxygenated and under anoxic conditions (Figure 3) demonstrate the classical oxygen effect. Removal of sublethal damage was determined at a single selected dose (8 Gy) in each case, by separating two equal dose fractions by a sufficiently long interval (1-1/2 h) to permit significant enhancement of survival. Removal of potentially lethal damage was determined at the same dose, by delaying the subculturing for the same interval. Two significant findings were observed. As illustrated in Figure 3, the production (or production and removal) of sublethal damage appears to be oxygen dependent; little split-dose survival enhancement is seen under anoxic conditions. In contrast, there appears to be little difference in the amount of potentially lethal damage removed under the anoxic and well-oxygenated conditions. This means that damage produced in anoxic irradiation must be potentially lethal in nature and is removed by processes that are probably not oxygen dependent.

These data support the hypothesis that sublethal damage and potentially lethal damage, as well as their respective damage removal processes, normally exist simultaneously, and that each type of damage is removed by an independent process.

FIGURE 3. Typical Survival Curves for Starved Plateau-Phase CHO Cells Irradiated Under Anoxic and Under Well-Oxygenated Conditions, Showing the Relative Amounts of Repair Observed by Split-Dose and Delayed-Plating Techniques. Note that split-dose irradiation results in no significant survival enhancement in the absence of oxygen.

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FLOW-CYTOMETRIC ANALYSIS OF PLATEAU-PHASE MAMMALIAN CELL POPULATIONS

J. M. Nelson, P. Todd,* and N. F. Metting

We have already shown that starved Chinese hamster ovary (CHO) cells accumulate in the G1 phase and, to a lesser extent, in other

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parts of the cell cycle, while fed cells continue to progress parasynchronously with a periodicity that reflects the feeding schedule (Nelson, Todd and Metting 1984). We have further characterized these kinetic differences by flow-cytometric techniques. DNA distributions were determined as a function of time by fixing trypsinized cells and staining them with the acriflavine-Feulgen procedure for DNA flow-microfluorimetric (FMF) analysis using an EPICS V cell sorter (Coulter Electronics, Inc.) located at Pennsylvania State University. The amount of DNA present and other related characteristics of cells from both fed and starved plateau-phase cultures were monitored as the cultures grew to confluence and then passed into late plateau phase. Additionally, 14-day-old fed and starved plateau-phase cultures were dispersed and the subcultured cells followed, as they passed through their first post-plateau-phase cycles.

Results of these studies verify and supplement our earlier work, which had been done using more classical cell-kinetic methods to characterize the equilibrium plateau-growth state. Analysis of the FMF measurements is complex and has resulted in the preparation of two separate papers, one of which is nearly ready for submission. Tentative titles of these two manuscripts are 1) "Growth activity in fed and starved plateau-phase cultures of Chinese hamster ovary cells; a flow cytometric study" and 2) "Reentry into the cell cycle by fed and starved plateau-phase Chinese hamster ovary cells; a flow cytometric study." Both will be submitted to *Cell and Tissue Kinetics* in the near future.

In addition to verifying the conclusions drawn earlier, these studies also verified the existence of nonincorporating S-phase cells in the starved populations. These cells have S-phase DNA content, even though they do not incorporate [^3H]TdR and probably are not synthesizing DNA.

As the starved cells grow into late plateau phase (over 8 days), cultures are found to consist primarily of G1-phase cells, with about 10% S-phase, and 7% G2-phase cells. Some cells have deficient DNA content. In contrast, fed cultures of about the same age are a mixture of cycling and noncycling cells, with the cycling cells progressing

synchronously in a manner reflecting the feeding schedule. As expected, these fed cultures seem to maintain this dynamic plateau phase by producing a population of dead cells that is detected as Feulgen-positive debris.

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Nelson, J. M., P. W. Todd, and N. F. Metting. 1984. "Kinetic Differences Between Fed and Starved Chinese Hamster Ovary Cells." *Cell Tissue Kinet.* 17(4):411-426.

KINETIC DIFFERENCES BETWEEN FED AND STARVED CHINESE HAMSTER OVARY CELLS

J. M. Nelson, P. Todd,* and N. F. Metting

When Chinese hamster ovary (CHO) cells are grown as monolayer cultures, they eventually reach a population-density plateau after which no net increase in cell numbers occurs. A manuscript has recently been published which draws attention to the important, and perhaps unexpected, differences in the kinetic status of different types of plateau-phase CHO cells (Nelson, Todd and Metting 1984). The essence of this manuscript and the most significant findings are summarized in the following paragraphs.

The kinetics of aged cells in nutritionally deprived (starved) or density-inhibited (fed) late plateau-phase cultures were studied by four methods:

1. Reproductive integrity and cell viability were monitored daily by clonogenic-cell assay and erythrosin-b dye-exclusion techniques, respectively.
2. Mitotic frequencies of cells from 18-day-old cultures were determined during regrowth by analyzing time-lapse video microscope records of dividing cells.
3. Tritiated-thymidine autoradiography was used to determine the fractions of DNA-synthesizing cells in cultures entering plateau phase and during regrowth after harvest.

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4. The rate of labeled nucleotide uptake and incorporation into DNA was measured by liquid scintillation or sodium iodide crystal counters after labeling with [^3H]TdR or [^{125}I]UdR.

Noncycling cells in starved cultures were found to accumulate primarily as G1-phase cells. Most cells not in G1 phase had stopped in G2 phase. Very few cells (<2%) were found in S phase. In contrast, about half of the cells in periodically fed cultures were found to be in DNA-synthetic phase, and the percentage of S-phase cells fluctuated in a manner reflecting the frequency of medium replacement. Populations of both types of plateau-phase cultures demonstrate extremely coherent cyclic patterns of DNA synthesis upon harvest and reculturing. They retain this high degree of synchrony for more than three generations after the resumption of growth. From these data we have concluded that nutritionally deprived (starved) late plateau-phase cells generally stop in either G1 or G2 phase, whereas periodically fed, late plateau-phase cultures contain a very large fraction of slowly cycling cells. Populations of cells from these two types of nonexpanding cultures are kinetically dissimilar and should not be expected to respond in the same manner to extracellular stimuli, e.g., hormones, mutagens, carcinogens, and exciting or ionizing radiations.

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Nelson, J. M., P. W. Todd and N. F. Metting. 1984. "Kinetic Differences Between Fed and Starved Chinese Hamster Ovary Cells." *Cell Tissue Kinet.* 17(4):411-426.

SURVIVAL OF SUBPOPULATIONS OF PLATEAU-PHASE CHINESE HAMSTER OVARY (CHO) CELLS SELECTED BY SIZE

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Most of the experimental radiation biology employed to test theoretical models of radiation damage uses cultured cells as the biological system and reproductive survival as

the biological endpoint. Although mammalian cells are most relevant from our point of view, their radiation sensitivity changes as a function of a cell's position in its replicative cycle, thus complicating the interpretation of experimental results. Exponentially growing populations are the most confusing, as the cells are distributed throughout G1, S, G2, and M phases, and most of the cells are moving through the cycle, changing sensitivities as they progress. Results from studies using plateau-phase cell populations are more easily interpreted, since each cell can be considered to be stationary in the cell cycle. However, it has also been shown (Nelson, Todd and Metting 1984) that even though ~85% of the cells are residing in G1 phase, the other phases are all represented. We use these starved, plateau-phase CHO cell populations in dose-rate, split-dose, and delayed-plating radiation response studies. Our work shows that two types of radiation damage repair are occurring simultaneously in this population, with repair half times of about one hour and twenty hours. It is possible that each repair rate reflects the same type of repair, but is manifested in different subpopulations at different rates.

One way to investigate this question is by irradiating a given population and then, using centrifugal elutriation, gently and aseptically separating it into subpopulations based on cell volume. Each fraction would then be assayed independently for its clonogenic potential. To be certain that the sizing criteria reflect the expected stages of the cell cycle, flow cytometry would be used to measure the DNA content of the cells in each fraction. This is the plan we have adopted. Preliminary work has already been done to perfect the elutriation technique for our experimental design, using a Beckman's JE-6B elutriation system and rotor. Modifications have been introduced that now provide greater assurance of sterile operation throughout the day-long experiments.

The average diameter of CHO cells in early G1 phase from an exponentially growing population is 12.6 μm , while those in late G2 have an average cell diameter of 15.6 μm . These values give corresponding cell volumes of about 1000 and 2000 μm^3 , implying that doubling the DNA content corresponds to a

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doubling of overall cell volume, under isotonic conditions. Allowing for the fact that the average cell volume found in plateau growth populations may be smaller, we are fractionating our cell populations in the range of 8 to 18 μm diameter. The presence of cells in the larger cell-size fractions is a measure of the cell multiplicity or cell clumping problem under these experimental conditions. This problem will have to be overcome and our flow cytometry capabilities implemented before detailed measurements can be obtained.

Preliminary results, illustrated in Figure 1, show that each of the individual subpopulations is more resistant to radiation than the total (unsorted) population. This may be a result of "cleaning up" the culture by the loss of the more fragile cells. The larger volume fractions are particularly resistant, but this may be an artifact of multiplicity. The survival after split irradiations, separated by 14 or 24 h, is essentially the same as that for the unsorted population. Furthermore, survival of the two smaller size subpopulations suggests that there is not a large difference in repair capacity between G1 and G2 cells.

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Nelson, J. M., P. W. Todd, and N. F. Metting. 1984. "Kinetic Differences Between Fed and Starved Chinese Hamster Ovary Cells." *Cell Tissue Kinet.* 17(4):411-426.

FIGURE 1. Survival Curves for Starved Plateau-Phase CHO Cells, Sorted According to Cell Diameter, Compared with the Unsorted Population.

• Modeling Cellular Response To Genetic Damage

This program is directed toward achieving a better understanding of the mechanisms by which alterations in mammalian cell chromosomes produce toxic and mutagenic effects. Understanding the role of cellular biochemical processes in the production and repair of genetic damage is a key element in developing a scientific basis to assess the risk of low-level exposure to radiation and chemical carcinogens. Through experiments in our laboratory with the rodent cell line CHO-K1, we have discovered unusual effects of mutagens on the cellular pool of molecules used in DNA synthesis and repair. Current efforts are focused on determining the biochemical mechanisms for pool imbalance induced by radiation and chemicals and the role of this imbalance in other cellular response to the exposure.

MECHANISM OF MUTAGEN-INDUCED DEOXYNUCLEOSIDE TRIPHOSPHATE IMBALANCE IN CHINESE HAMSTER OVARY (CHO-K1) CELLS

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In previous reports (Newman and Miller 1983a, 1983b, 1983c), we demonstrated that exposure of Chinese hamster ovary cells (CHO-K1) to chemical carcinogen or radiation insults results in a transient deoxynucleoside triphosphate (dNTP) pool imbalance. Such an imbalance might be expected to affect the mutagenic response of cells to exposure by increasing the probability for base-misincorporation into *de novo* synthesized DNA (Meuth 1981; Meuth 1984; Ashman and Davidson 1981), and/or by exerting regulatory controls over the replicative response to exposure (Nicander and Reichard 1981; Newman and Miller 1983a). Indeed, we show in Table 1 that a marked reduction in UV-induced mutations to thioguanine-resistance (TG^R) in CHO-K1 cells can be effected by simply altering the ratio of deoxycytidine triphosphate

(dCTP)/thymidine triphosphate (dTTP); this is accomplished by adding deoxycytidine (CdR) to the growth medium.

Exposure to UV irradiation, a model mutagen, results in a rapid decrease (five- to tenfold) in cellular dCTP and a concomitant increase (three- to sixfold) in dTTP, each observed within 10 minutes of exposure, and each persisting for several hours thereafter. These results, which appeared in last year's annual report, have now been published (Newman and Miller 1983b). However, the target and mechanism causing this response are not defined and, therefore, are presently the object of considerable study. Figure 1 illustrates the pathways of intermediary metabolism that normally impact the synthesis and degradation of dCTP and dTTP. A working hypothesis, now corroborated by data, is that radiation induces perturbations in selected enzyme activities which then perturb prevailing steady-state reaction equilibria, which, in turn, result in the imbalance we observe. Key enzyme activities were, therefore, examined in irradiated cells and compared to corresponding activities observed in unirradiated cells.

TABLE 1. Response to UV ($10Jm^{-2}$)

Growth Medium ^(a)	Do (Jm^{-2})	TG^R Mutants/ 10^5 Survivors
Complete	10.5	250
Complete + 2 mM Cd ^R	7.8	23

(a) Complete medium consists of Ham's F-12 + 10% fetal calf serum.

No UV-induced increases were observed in thymidine (TdR) kinase and thymidylate (dTMP) synthase activities (Figure 2). In particular, the lack of change in thymidine kinase activity suggests that the rapid increase in dTTP is not due to an accelerated conversion of exogenous thymidine to its phosphorylated forms. Therefore, the increase in dTTP after UV must arise from an increase in cellular dUMP, the substrate for thymidylate synthase. To ascertain the source of dUMP, the effects of UV on other enzyme activities were examined. These analyses revealed significant

FIGURE 1. Pyrimidine Metabolism in Mammalian Cells. Double arrows indicate reversible steps; single arrows indicate irreversible steps; dotted arrows show reactions not present in some cell lines.

FIGURE 2. TdR Kinase and dTMP Synthase Activities in CHO-K1 Cells After UV. Activities are normalized to those observed in unirradiated controls. (□, Δ, ○) immediately after exposure; (■, ▲, ●) after a 10-min post-irradiation incubation in complete growth medium.

increases in dCTPase, CdR kinase and dCMP deaminase activities associated with exposure to radiation (Figures 3 and 4). In combination with one another, these altered activities would be expected to increase cellular dUMP while simultaneously diminishing the dCTP concentration. This is consistent with observations on changes in dCTP and dTTP concentrations noted earlier, and strengthens

FIGURE 3. dCTPase Activity in CHO-K1 Cells After UV. Relative product yields from $[5\text{-}^3\text{H}]\text{dCTP}$ substrate are normalized to dCMP + dUMP in unirradiated control. Open symbols and closed symbols are as described in Figure 2.

the hypothesis that these mutagen-altered enzyme activities are responsible for induction of dNTP imbalances. It is noteworthy that enhancement of dCTPase activity is greater when cells are harvested immediately

FIGURE 4. dCMP Deaminase and CdR Kinase Activities in CHO-K1 Cells After UV. Activities are normalized to those observed in corresponding unirradiated controls. (---) dCMP deaminase; (—) CdR kinase; open symbols and closed symbols are as described in Figure 2.

after irradiation, in comparison to activity observed 10 min later (Figure 3). This observation further implies that irradiation induces a short-lived activation of this enzyme, an interpretation which is consistent with observations of the kinetics of UV-induced pool imbalances, as reported earlier (Newman and Miller 1983b).

While mutagen-induced pool imbalances appear to be universal, occurring in all procaryotic and eucaryotic cell systems thus far examined (Das et al. 1983; Das et al. 1984; Suzuki et al. 1983; Newman 1983a, 1983b), the nature of the imbalance often differs. In Chinese hamster V-79 cells, for example, there is little change in dCTP, while dTTP concentration increases are observed only hours after exposure (Das et al. 1983). Examination of the aforementioned enzyme activities in V-79 cells reveals that these cells contain no dCMP deaminase (Table 2). The absence of this enzyme would therefore preclude the conversion of dCTP to dTTP by the mechanism

TABLE 2. dCMP Deaminase Activity

Cell Line	Enzyme Activity ^(a)
CHO-K1(b)	10.9 ± 0.2
CHO-K1(c)	1.3 ± 0.2
CHO-K1(d)	0.28 ± 0.36
V-79(e)	0

- (a) Determined in growing exponential-phase cells. Activity is expressed as % [³H] from [³H]dCMP as dUMP/A595 (protein) ± standard deviation.
 (b) CHO-K1 laboratory stock, obtained from M. Frazier, Pacific Northwest Laboratory.
 (c) CHO-K1 obtained from John Nelson, Pacific Northwest Laboratory.
 (d) CHO-K1 pro⁻ (Meuth 1981), obtained from Craig Spiro, Oregon State University.
 (e) V-79 provided by Philip Liu, University of Washington.

we propose for our CHO-K1 cells and would thus explain the contrasting dNTP pool response to exposure in the two cell lines. Table 2 also shows that dCMP deaminase activities vary among CHO-K1 cell lines obtained from this and other laboratories; the magnitude of the dCTP/dTTP imbalances induced by irradiation probably varies accordingly. These differences will be exploited to ascertain the significance of this regulatory process on the biological response of cells to radiation and chemical mutagens.

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STOCHASTIC REPAIR-MISREPAIR MODEL

J. H. Miller

The potential to quantitate both damage and mutation at the molecular level opens the possibility for stochastic simulation of mutation induction. The model described below is based on the hypothesis that mutations induced by physical and chemical mutagens result from errors in DNA replication because of damage in the parental template.

In bacteria it is meaningful to distinguish "direct" and "indirect" effects of DNA damage. Miscoding due to distortion in the DNA helix near a covalently bound adduct is an example of a direct effect. However, DNA damage may also induce responses (e.g., SOS repair) that involve mutator genes (Witkin 1976). This indirect effect of DNA damage may account for the low correlation between DNA binding spectra and mutation spectra observed in some experiments (Fuchs 1983).

At present, there is no evidence for an SOS-type response in mammalian cells. Nevertheless, mammalian cells do tolerate DNA damage and it is frequently speculated that the process by which the replication complex (replisome) bypasses DNA damage is error-prone. In this model the consequences of replication on damaged templates are treated stochastically (i.e., by random variables). The probability distributions that govern the possible outcomes of damage-replisome interactions are the primary input to the model. This information is far from complete; however, formulation of the model will serve to focus on the data needs and perhaps will stimulate new experiments.

Damage in DNA is not static. In addition to the error-prone process that allows synthesis of daughter strands on damaged the template, the cells also restore the template prior to replication. We assume that the latter component of repair is catalyzed by enzymes (distinct from the replication complex) that recognize damage, restore the genetic information (e.g., excision of adducts, strand rejoining, etc.), and dissociate from the DNA. This type of repair could also be treated stochastically with outcomes other than perfect restoration of the parental strand; however, for simplicity we will assume this repair is error-free and a deterministic function of the time elapsed since damage induction.

Calculation of the frequency of mutations induced in a particular DNA sequence would involve the following steps:

1. Select a damage realization (i.e., a distribution of damage sites that simulates exposure at a given dose). For the purpose of this discussion we will assume a high dose rate but the model could be extended to include time delays between

damage induction. In the absence of other information one could assume a uniform distribution of damage sites; however, this will not be adequate in many cases due to preferential binding of adducts and shielding that result from chromosome structure.

2. Allow the replitase to interact sequentially with each damage site. At each replitase-damage encounter, choose a delay that is consistent with the inhibition of chain elongation by the DNA damage at the dose being simulated. Delays plus travel time between damage sites determine the total time elapsed since damage induction and hence the extent of error-free repair. The consequence of restricting error-free repair at the replication fork can be investigated.
3. Some constraint on the total time available to replicate the gene should be included in the model. If the delay chosen in the above step causes this time to be exceeded, terminate the case history and select another damage realization. Otherwise, proceed to the next damage site after selecting a complementary base or no base. If the selected base pairing is incorrect, score a mutation at the damage site.
4. After N sequential encounters with damaged sites, return to the first step and choose

another damage configuration. If the mutagenic potential of the damage is fixed at the first mitosis, then $N=1$. Ultimately N must be limited by mutation selection procedures.

The absolute frequency of mutations observed in a given gene depends on the cellular response to damage in other regions of DNA and probably non-DNA damage as well. Hence this model can predict only relative mutation frequencies at different points in the gene (mutation spectra), with different cell strains (repair mutants), and under different exposure conditions. The main advantage of a stochastic treatment is that mutation induction is a rare event and hence cannot be adequately modeled in terms of averaged properties of the DNA damage. Stochastic simulation allows us to explicitly consider rare damage configurations that may challenge the cell's repair capacity.

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• Internal Microdosimetry

The purpose of this study is to develop practical methods for calculating microdosimetric distributions for plutonium or other alpha-emitting elements that are deposited internally, especially as particulates, in soft tissue and lung tissue. This study will aid the correlation and extrapolation of radiation effects measured at different levels of exposure, different distributions in dose and in different species. Computational methods are developed and tested in the Radiological Physics section. Concurrently, the Dosimetry Technology section develops cell and tissue models in which those methods are applied. During the past year, progress was made in adapting the internal microdosimetry computer codes for application on a VAX computer and in significant improvements in the codes. Cell studies were completed that provide definitive tests of the theoretical concepts and progress was made in improving the theoretical basis for calculating energy deposition by inhomogeneous sources.

ALPHA-PARTICLE DOSE DISTRIBUTION EFFECTS AT THE CELLULAR LEVEL

D. R. Fisher, M. E. Frazier, and
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Ionizing radiations that differ in number, size, and distribution of energy deposition events might be expected to cause different effects for the same absorbed dose. Furthermore, microdosimetry calculations suggest that large variations in biological effectiveness might be expected for internally deposited alpha-emitting radionuclides for the same absorbed dose, depending upon the specific activity and spatial distribution of the sources in tissue. The study described in this article was designed to demonstrate these phenomena in vitro.

The important influence of dose distribution from alpha-particle radiation was demonstrated last year (Fisher and Frazier 1984). Preliminary results showed that different levels of cytotoxicity could be observed for alpha radiation from particulate sources compared to uniformly distributed sources or ^{60}Co gamma rays.

The experiments begun last year were continued and expanded. Cultured Chinese hamster ovary (CHO-K1 BH4) cells were exposed in vitro to inert, insoluble ceramic microspheres of zirconium dioxide labeled with ^{239}Pu .^{*} The average exit energy of the

5.15 MeV alpha particle was calculated to be 4.3 MeV. Exposure times varied from four to seven hours to achieve the desired dose level.

The CHO cells and $^{239}\text{PuZrO}_2$ microspheres were mixed, forming a planar geometry on the bottom surface of plastic culture dishes measuring 25 cm² (Figure 1). The cells and microspheres were separated by centrifugation at the end of the exposure period.

Cells were exposed to hot particles, uniformly distributed alpha-particle radiation, and ^{60}Co gamma radiation. A nearly uniform distribution of alpha-emitting ^{239}Pu was achieved by gently rocking one group of culture dishes during the exposure period; the rocking motion caused the microspheres to roll about on the bottom of the dishes while the CHO cells remained attached. Approximately 10^6 cells per dish were exposed.

Biological endpoints studied included cell survival, mutation rates and primary DNA damage. Initial survival was determined by a clonal growth assay. The mutation assay involved scoring for specific mutations at the HGPRT locus. The alkaline elution technique was used to determine the frequency of single-strand DNA breaks.

Absorbed doses were calculated by determining the mean specific energy imparted to CHO cell nuclei for each exposure condition. The mathematical methods of Roesch (1977) for internal microdosimetry were employed. Cell

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Laboratory, Los Alamos, New Mexico.

FIGURE 1. A Schematic Cross-section of the Planar Exposure Geometry for Cultured CHO Cells and Zirconium Oxide Microspheres.

nuclei were assumed to be spherical (dia. = $9.0 \mu\text{m}$) and randomly distributed with respect to the radioactive sources.

The number and distribution of microspheres per dish were determined by photomicrographs. The emitted radiation was also measured by a 3-in. NaI(Tl) crystal detector and multi-channel analyzer.

Survival and mutation frequencies for CHO cells given one of six different exposure regimens are shown in Table 1. The initial

survival is expressed as a percent of the sham-exposed control group. Mutation frequency was expressed as mutant clones per 10^6 viable cells, and 2.5×10^6 cells were evaluated for mutation at the HGPRT locus. Triplicate samples for each group were processed. The estimated percentage of cells hit by alpha radiation was determined by computer calculations.

The results of this work show that mutation frequency increased with increasing uniformity of the dose distribution from alpha

TABLE 1. Effects of Alpha and Gamma Radiation on Initial Survival and Mutation of CHO Cells

Radiation Type	Number of Spheres	Condition	Absorbed Dose (rads)	Initial Survival		Mutation Frequency		Percent Hit
				Experiment A	Experiment B	Experiment A	Experiment B	
Alpha Radiation:								
0.07 pCi Spheres	1.9 x 10 ⁶	Stationary	70	67	72	6.4	8.0	57.4
	1.9 x 10 ⁶	Agitated	70	74	59	23.8	32.1	85.5(a)
1.87 pCi Spheres	7.1 x 10 ⁴	Stationary	70	94	94	7.3	5.6	6.6
	7.1 x 10 ⁴	Agitated	70	103	87	18.4	19.9	85.5(a)
Gamma Radiation:								
External ⁶⁰ Co	None	--	70	95	93	12.3	6.8	100
Controls:								
ZrO ₂ Spheres	1.9 x 10 ⁶	Agitated	0	100	100	4.5	1.2	0

(a) Assumes a completely uniform alpha particle dose distribution.

particles. Stationary microspheres were less mutagenic than an equivalent absorbed dose from ^{60}Co gamma radiation, and much less mutagenic than agitated microspheres.

Cell killing was greater for microspheres of low specific activity than for high-activity microspheres. There was no statistically significant difference between the effects of stationary and agitated microspheres. The results also show that we did not obtain a completely uniform dose distribution by agitation or mixing of microspheres; thus, it is unlikely that the same number of cells were hit by agitated microspheres of high and low specific activity. Mixing was more thorough in Experiment Series B.

The same exposure regimen was followed in a study of primary DNA damage, with each group receiving an absorbed dose of 70 rads. Single-strand breaks were measured by alkaline elution at 4°C in darkness. The amount of eluted DNA was determined fluorometrically.

Figure 2 shows that alpha radiation from ^{239}Pu caused single-strand breaks in CHO cell DNA and that the degree of damage depended upon spatial distribution of the alpha-particle dose. Increasing amounts of DNA damage were produced with increasing uniformity of the dose distribution. Hot-particle sources were less effective than ^{60}Co gamma radiation in producing single-strand DNA breaks.

These results confirm earlier findings that response to alpha-particle radiation is more than simply a function of absorbed dose. The spatial distribution of sources and the activity of individual sources influence the percent of cells hit by alpha particles and the frequency of multiple hits. Hot particles hit fewer cells, but do so with more hits per cell.

These results also show variable relative biological effectiveness (RBEs) for alpha emitters. RBEs were found to vary from <1 to about 7 compared to ^{60}Co , depending upon the exposure geometry and the endpoint considered. Indeed, dose distribution from internally deposited radionuclides should therefore be an important consideration in

FIGURE 2. Effect of Alpha and Gamma Irradiation on the Alkaline Elution Characteristics of CHO-K1 Cell DNA, with Alpha Particle Distribution and Specific Activities as Modifying Factors.

evaluating biological damage at the cellular level. Further work will be required to correlate specific energy distributions with the biological endpoints observed in this study.

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IMPLEMENTATION OF MICRODOSIMETRY CODES ON MINI-COMPUTERS

R. T. Hadley, W. E. Wilson, and D. R. Fisher

Computer programs (codes) are required to perform the complex mathematics of internal microdosimetry. Specific energy distributions for internally deposited alpha-emitting radionuclides can be calculated with these codes.

The original internal microdosimetry computer codes were designed primarily for evaluation of theoretical formulations. They were written by W. C. Roesch for a large mainframe computer with input variables entered by punched cards. Since then, the codes have been continuously updated and revised to meet changing needs and adapted to more modern computer systems.

During the past year, the code MICRO was implemented on a supermini-computer system. MICRO calculates probability densities in specific energy for various geometrical configurations of sources (radioactivity) and sites (biological targets) in unit-density media. Implementation of MICRO involved upgrading a previous FORTRAN code, adding new display and printer graphics commands, and upgrading the user-interface with the computer to allow either interactive- or batch-mode execution of the computer programs.

A newer FORTRAN code, LUNG, was also completed during the past year. LUNG calculates the microdosimetry of alpha-emitting sources in the dog lung, using a unique model of lung tissue microstructure (Fisher, Hadley and Roesch 1982). The original version of LUNG was written in BASIC language and designed to run on a small desktop microcomputer. In revising LUNG, we added a set of subroutines, including new display graphics and a user-interface. The mathematical operations of the code were verified.

LUNG operates on the assumption that all particles inhaled by the dog are of uniform size and activity and are not cleared from the lung with time. A new code, DOGLUNG, was therefore written to allow use of known aerosol particle size distributions. DOGLUNG also allows the user to specify the biological retention half-time for the material deposited in the lung. This code is being

applied to the study of the correlation between specific energy density and long-term biological effects in the dog from inhaled plutonium oxide.

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AVERAGING DOSE IN INHOMOGENEOUSLY IRRADIATED TISSUE

W. C. Roesch

In doing dosimetry for radiation protection, time and cost usually lead us to settle for just one, or a few measurements of the dose a person might receive. Economy similarly dictates that single doses be used in many epidemiological studies. Even in laboratory studies in radiobiology, where complete depth dose curves may be obtained, results are frequently summarized by citing single doses or average doses. These single doses sometimes have to represent situations in which the dose throughout an individual or an individual organ may be quite inhomogeneous, i.e., the dose may have a wide range of values.

In many cell-culture experiments, if the dose is not too high, the effect, E , is found to be a linear-quadratic function of the dose, D ,

$$E = A D + B D^2 \quad (1)$$

In these experiments, the dose is uniform throughout the culture. If similar expressions are assumed to hold for cells receiving the same dose in vivo, then the average (denoted by $\langle \rangle$) effect in a tissue where the dose is inhomogeneous is

$$\langle E \rangle = A \langle D \rangle + B \langle D^2 \rangle \quad (2)$$

In other words, the corresponding averages for both the dose and the square of the dose

have to be known to relate the observed effect to that found *in vitro* or to compare effects in different tissues.

When a single dose, d , is used to characterize an exposure, Equation (2) can be changed to

$$\langle E \rangle = A \left[\frac{\langle D \rangle}{d} \right] d + B \left[\frac{\langle D^2 \rangle}{d^2} \right] d^2 \quad (3)$$

If the quantities in brackets are independent of dose, this expression says that the observed effect will also be linear-quadratic in the single dose used. This is often the case, at low doses, for mutation and oncogenesis in small animals. Calculations were made of the bracketed quantities for conditions simulating irradiation of the skin (Roesch 1984). The results depend on just what the dose, d , represents. The range of values for the quantities can cover as much as an order of magnitude. Thus, their evaluation must be an important part of comparative studies of skin effects.

The means used here are mean values over spatial inhomogeneities. In addition, there are microscopic inhomogeneities due to stochastic phenomena that are the subject of microdosimetry. The two can be combined by combining their variances.

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MONTE CARLO CALCULATION OF ENERGY DEPOSITION AND IONIZATION YIELD FOR HIGH ENERGY PROTONS

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The stochastic distributions of ionization and energy deposition in small volumes (volumes less than a few tenths of a micron in

diameter) by charged particles are of importance to the dosimetry of internal alpha emitters. The calculation of these distributions and parameterization of their systematics is a major activity since the results will be useful in other dosimetry areas as well. One such application is introducing straggling into event-size spectra for neutrons. Recent calculations of event-size spectra for neutrons use a continuous slowing down approximation model for the energy losses experienced by secondary charged particles (protons and alphas) and thus do not allow for any straggling effects (Caswell, Coyne and Goodman 1981; Coyne et al. 1981). Discrepancies between the calculations and experimental measurements are thought to be, in part, due to the neglect of straggling. A tractable method for including stochasticity in the radiation transport calculations is the Monte Carlo method; a number of efforts toward simulating positive ion track structure have been initiated. We have made recent progress using our updated and extended MOCA code for charged particle track structure (Wilson and Paretzke 1981). Major emphasis has been on calculating energy deposition and ionization yield spectra for recoil proton "crossers" since they are the most prevalent event type at high energies (~99% at 14 MeV) for small volumes. Neutron event-size spectra can then be obtained from them by numerical summing and folding techniques. Results for energy deposition and ionization yield have been obtained for simulated proton tracks of 0.3 to 20 MeV in spherical sites of diameters 2 to 1000 nm.

Spectra are recorded for tracks passing at varied distances (eccentricities) from the center of the site out to about 1.5 times the site radius. A brief selection of the extensive data computed to date is presented in Figure 1. Probability functions, sometimes called sum distributions, for the number of ionizations are plotted for diametric (solid lines) and tangential (dashed lines) paths for 0.3 to 10 MeV protons and a 100 nm diameter site. As plotted here, the ordinate and abscissa are each transformed to make a log-normal distribution appear as a straight line. The curves suggest that, except perhaps for tangential paths at low energy, a log-normal distribution may be an adequate empirical representation of the data for many applications.

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FIGURE 1. Ionization Sum Distributions for 0.3 to 10 MeV Protons in a 100 nm Diameter Site. Solid lines are for ion paths passing diametrically through the site, dashed lines are for tangential paths. (A log-normal differential distribution would plot as a straight line on this graph.)

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N. A. Wogman (10)
Technical Information (5)
Publishing Coordination (2)