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RADICAL PRODUCTION IN BIOLOGICAL SYSTEMS

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Introduction

This paper describes our effort to develop a metric for radiation exposure that is more fundamental than adsorbed dose and upon which a metric for exposure to chemicals could be based. This metric is based on the production of radicals by the two agents.

Radicals produced by radiation in biological systems are commonly assumed to be the same as those produced in water despite the presence of a variety of complex molecules. This may explain why the extensive efforts to describe the relationship between energy deposition (track structure) and molecular damage to DNA, based on the spectrum of radicals produced, have not been successful in explaining simple biological effects such as cell killing. Current models(Goodhead, 1992) assume that DNA and its basic elements are immersed in water-like media and only model the production and diffusion of water-based radicals and their interaction with DNA structures; these models lack the cross sections associated with each

macro-component of DNA and only treat water-based radicals. It has been found that such models are not realistic because DNA is not immersed in pure water(von Sonntag, 1987).

A computer code capable of simulating electron tracks, low-energy electrons, energy deposition in small molecules, and radical production and diffusion in water like media has been developed. This code is still in at a primitive stage and development is continuing. It is being used to study radical production by radiation, and radical diffusion and interactions in simple molecular systems following their production. We are extending the code to radical production by chemicals to complement our PBPK modeling efforts(Jarvis et al, 1992; Thrall et al, 1992). It therefore has been developed primarily for use with radionuclides that are in biological materials, and not for radiation fields.

Computer Code

The modular approach of the code is shown in Figure 1, and the modules are discussed below.

The Monte Carlo code is divided in two basic modules in order to have a consistent approach to assess energy deposition patterns and chemical outcome on biological systems. The first module is based on physical models for electron transport (track structure); we use the basic principles of single scattering to assess energy deposition in simple molecules. A database was generated containing the cross sections for many

well known molecular structures in DNA such as small proteins and amino acids.

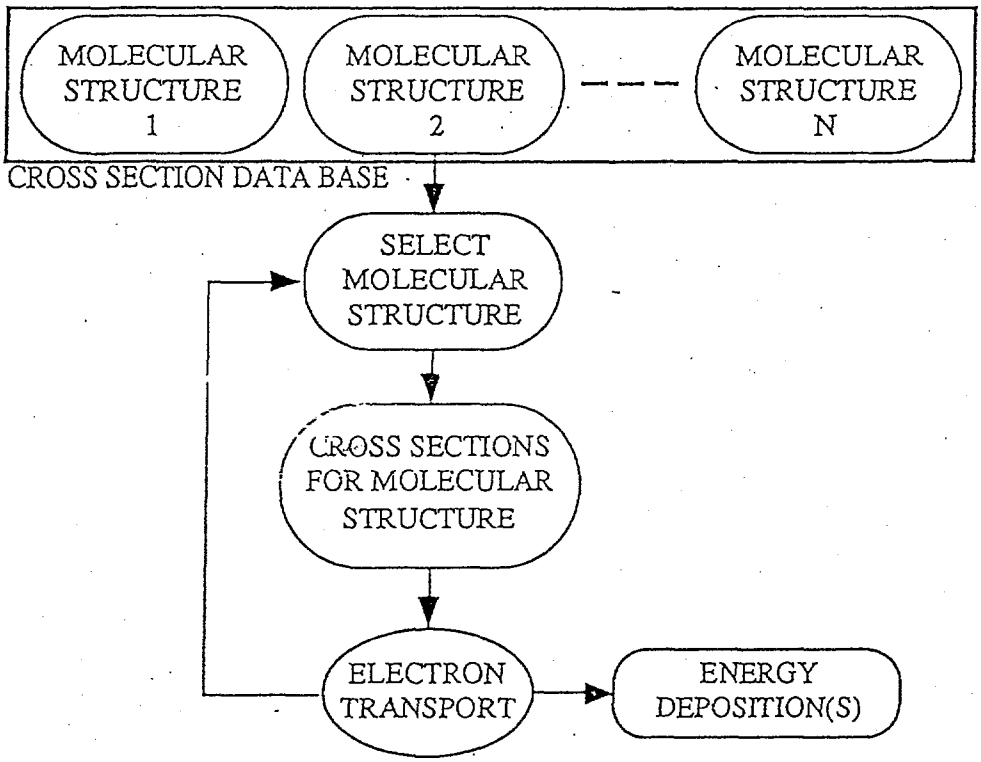

Figure 1. Physics module for the transport of electrons in molecular\ structures based on density concentration

Molecular Structure DataBase

The code require the user to select a molecular structure from the data base. Molecular structures(simulated in computer

code) have been obtained from several sources such as the International Nucleotide Sequence Database (Japan), Protein Data Bank (Brookhaven National Laboratory) or the National Center for Biotechnology Information (NIH). Even though there is a large number of molecules to consider, they can be simplified by reducing them by homology to a basic structure on which calculations can be done. This approach is consistent with our needs. The dynamics of the problem and macromolecules in DNA is too complex for our studies. These simplified molecules are then characterized in terms of probability of dissociation, recombination, and phonon and fluorescence production.

Physics Module

This module (Figure 2) simulates the physical processes that can occur following ionization as electrons interact with atoms and molecular structure of the selected molecule. The most commonly observed damage to cells following irradiation is base damage and DNA strand breaks(Cleaver, 1992). This damage results from processes involving initial energy deposition (track structure), radical formation and radical reactions. By determining the energy deposition patterns and the simulation of the energy transfer to molecules, radical production and diffusion, and the dissociation of large molecules can be modeled. The results of this modeling is the generation of new molecular species and the correlation of molecular changes with DNA damage.

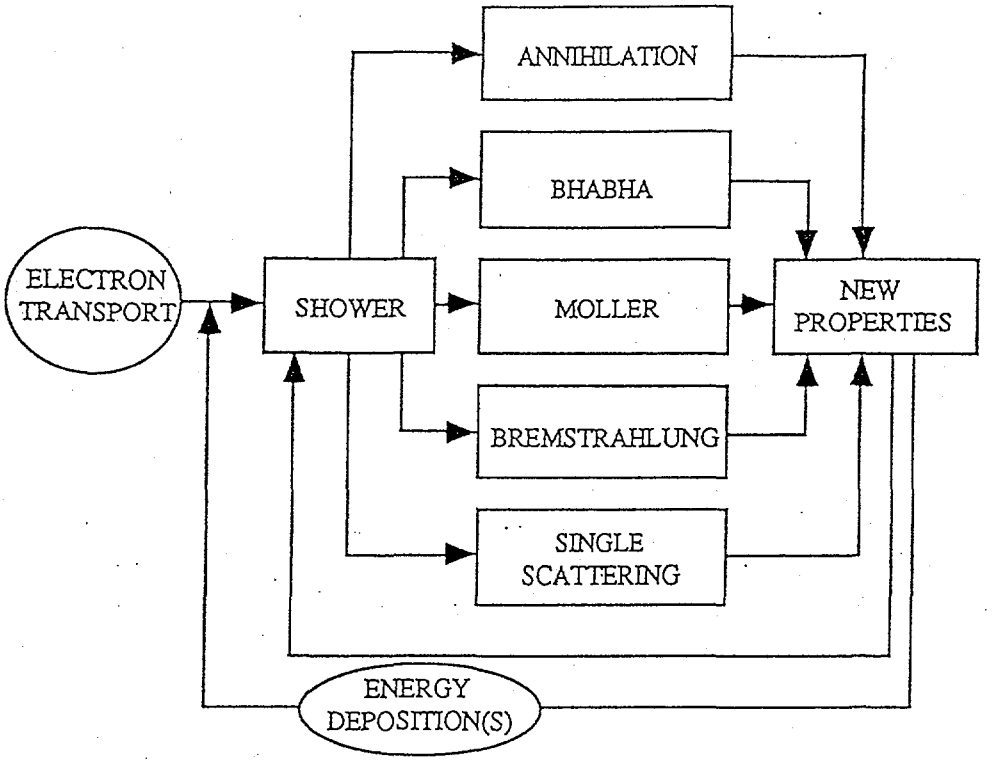

Figure 2. Flow chart of electron transport.

Chemistry Module

This module is shown schmatically in figure 3. DNA damage following exposure of cells to chemicals is similar, except for the initial energy deposition and radical production. Every specific molecule is characterized in terms of its probability of molecular dissociation, recombination, vibrational energy dissipation, fluorescence, and phonon production. Every phenomenon has an associated probability which is randomly selected based on initial radical interaction and available energy.

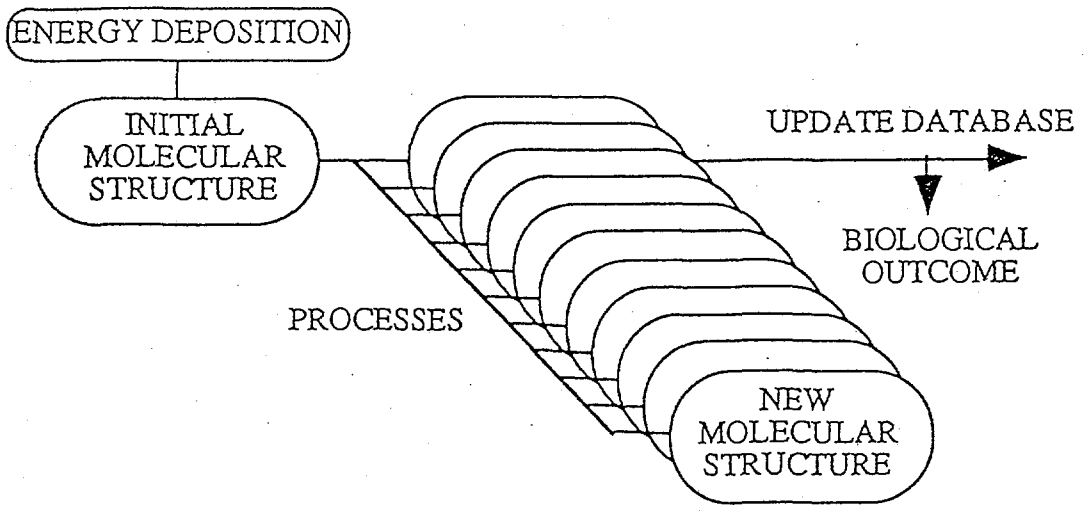

Figure 3. Chemical module for the determination of new molecules and their outcome.

the existing database. If a new molecular specie has been formed, it is included in the initial database to then allow it to become part of the overall molecular pool. This process is important with high dose rate exposures when large amounts of new molecular structures are generated in small time periods. In this case the chemical process is completely changed.

Discussion

The ICRP and the NCRP have both endorsed the "total detriment" (TD) concept for radiation protection in their most recent recommendations(ICRP, 1991; NCRP, 1993). This concept involves

converting risks to a common unit so that they can be added and compared to other risks in society. The common unit used by these organizations is the "length of life lost" from fatal cancers and severe genetic effects. Non-fatal cancers are included by weighting them with a "quality of life" factor. This process results in their recommendations on dose limits being given in "Effective" dose units. This quantity is derived from "Absorbed Dose," but it is actually a risk unit.

Their charters do not include protection from exposures to toxic chemicals, but a natural and necessary extension of the TD concept in protection is to include them. At present, this is difficult because there is no equivalent concept to absorbed dose for chemical exposures on which "chemical risk" factors can be based. This extension will be more important if the preliminary finding of Claycamp and Luo(1994) that plutonium will cause chemically induced oxidative DNA damage is confirmed by others.

Both chemicals and radiation interact with DNA by the production of radicals, and this process could be a methodology of adding the risk from chemical exposures into the TD concept of protection.

Conclusion

The fundamental objective of this code development is to provide testable predictions on radical production by radiation and by chemical and their interactions with DNA. These tests will lay the foundations

upon which a metric of risk from the separate or combined exposure to radiation and chemicals could be based. The code development is nearly complete, and work with others to develop and test predictions has begun.

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