DNA Core Ionization and Cell Inactivation

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INTRODUCTION

Ionizing radiation is known to cause damage to DNA molecules that can lead to cell death or cell inactivation. It is well understood that energy deposition by ionizing radiation at various DNA sites, such as sugars and bases, can lead to permanent molecular changes, and some of those are known to be the initiating events for the inactivation process. By probing with different types of heavy ions at different initial energies, it was demonstrated experimentally that the inactivation cross section increased with the increase of the linear energy transfer (LET), reached a maximum at a certain LET and then decreased continuously with further increase in LET (1). This phenomenon could not be explained on the basis of clusters of energy depositions presumed to generate clusters of damages to sugar and base molecules (2).

To explain the maximum in the inactivation cross section, we had suggested that the damages needed to be examined at the level of the atoms within the sugar and base molecules (3). Indeed, for a large range of energetic ions, we had demonstrated a striking correlation between the inactivation of various cells and inner-shell ionization cross sections in carbon, nitrogen and oxygen of the DNA molecule. Inner-shell ionizations trigger the so-called core events. Core events result from the multiple charges left in situ plus two low-energy electrons: the secondary and Auger electrons in the case of core events induced by fast electrons and the photo- and Auger electrons in the case of core events induced by ultrasoft X rays. These electrons individually have hundreds of electron volts and can be quite damaging by depositing a larger amount of energy within a small volume as they undergo multiple scattering. We have adopted a damage mechanism proposed by Fayard et al. (4). According to this mechanism, the occurrence of a core event in a DNA atom may cause several types of lesions in the DNA. The sugars or bases in which the atom is located are likely to be damaged efficiently because of the coulombic effect and charge neutralization. This mechanism can be identified as a direct effect. The secondary photo- and Auger electrons can cause additional base damages and multiple DNA strand breaks. Indeed, the two secondary photo- and Auger electrons can produce water radicals in the vicinity of the DNA. Such indirect effects of Auger electrons have already been observed in the case of DNA-incorporated radionuclides (5). Hence the indirect effects related to core events can be reduced by protective agents.

The phenomenon of core ionization also includes comparatively less frequent L-shell events in atoms such as phosphorus and sodium that are located in the backbone of DNA. The K-shell (or L-shell) ionization cross sections reach a maximum for ion velocities near the K-shell electron velocities, and hence the cross section is lower at velocities below or above this critical parameter. It has been shown that the ion velocities corresponding to LETs for which inactivation cross sections are maximum roughly match the K-shell electron velocities for carbon and oxygen (3).
To demonstrate the importance of core events, ultrasoft X rays have been used by tuning their energies to these near the various K-shell and L-shell ionization potentials. The energies can be selected to be either below or above the threshold of the K-shell or L-shell binding energies. By varying the X-ray energy above a given K-shell threshold, it is possible to produce a specific type of Auger electron. This allows the choice of the energy of the secondary electron that in turn allows simulation of various categories of core events produced by energetic electrons (4). We demonstrated that the biological efficiencies can be manipulated by varying the energies around the respective K-shell thresholds of carbon and oxygen (4, 6). For energies of soft X rays between 290 eV and 540 eV that are just above the K-shell threshold for carbon atoms and just below the K-shell threshold for oxygen atoms, the number of DNA core events for a given dose in a cell is about two times larger than outside this range. This effect is due to an abundance of carbon atoms that is about three times larger in DNA than in the surrounding medium within the cells. Hence, within this energy range, there will be a sharp increase in the biological effects. It is customary to express the relative efficiencies of a given radiation by comparing its effects for a given biological end point, such as cell survival, to that of standard 60Co γ rays. The ratio of the relative doses of the two radiation qualities needed to obtain the same level of cell survival is known as the RBE. Within the energy range mentioned above, there is a sharp increase in RBE demonstrating the phenomenon as well as the importance of core events.

Three experiments were performed at a synchrotron facility in Orsay, France, with V79 cells (4, 5). From the data presented in ref. (4), it is evident that the RBE increased by a factor of two as the energy of the ultrasoft X rays varied from 250 eV to 340 eV. The results were reproduced in an experiment with a human cell line B3 cells.2

The phenomenon of core ionization has not gained prominence due to the fact that compared to outer-shell ionizations these events occur much less frequently. For example, compared to fast ions, fast electrons and ejected electrons from γ rays and X rays, the core ionization phenomenon may amount to only several thousandths of the total number of events, but their biological consequences, such as cell inactivation, can be many orders of magnitude higher. In the past, to explain certain experimental observations for ultrasoft X rays, both the outer-shell ionizations and the core ionizations on DNA were included collectively, which failed to explain the biological efficiencies of these types of X rays. This method of analysis overlooked the independent contribution of the core events (7).

In this study, we have calculated the independent contribution of the core ionization process to the lethality of fast electrons and γ rays. With this in mind, the probability that a core event on DNA leads to cell inactivation (called lethal efficiency) is first estimated. This estimation is based on existing survival curves for ultrasoft X rays. For this purpose we made an assumption that the lethality of these types of radiations is entirely due to their production of core events on DNA (“core model” of lethality). This assumption is based on the correlation between the RBE of these particles and their production of core ionizations on DNA around the carbon K-shell threshold. It is then verified by comparison of the lethal efficiencies of phosphorus L-shell ionizations either calculated with this model or directly extracted from published experimental data. For any kind of particle, the knowledge of the lethal efficiencies of the core events created on DNA together with a Monte Carlo simulation of core ionizations in the particle track allows the determination of the yields of lethal events triggered by the sole core ionization process (“core” lethal events). The calculation is performed here for fast electrons and γ rays. The fractional contribution of core events to the lethality of these particles is then calculated as the ratio of the yields of core events and the total lethal events induced.

MATERIALS AND METHODS

An Expression for Mean Lethal Efficiencies of Specific Core Events

To assess the contribution of core events to lethality in the case of fast electrons and γ rays, it is necessary to extract the mean lethal efficiency of core events produced by an X ray of any energy. We briefly recall a mathematical expression previously derived in ref. (4) to include known experimental data.

Let us denote a core event by a pair of energies (E_A, E_S) where E_A and E_S, respectively, refer to the Auger and secondary electron energies. Let us also define Y(E) as the mean yield of lethal events per gray due to a mean yield of core events per gray, Y_A(E), where E = E_A + E_S, Y(E) can be calculated from experimental survival curves using the following relationship:

\[ S = \frac{1}{10} = e^{-Y_{core}(E)} \]

(1)

where D_0 is the dose corresponding to 10% survival. Since ln 10 = 2.3, it becomes

\[ Y(E) = \frac{2.3}{D_0(E)} \]

(2)

For 60Co γ rays, a D_0 value of 7.2 Gy for cell inactivation was used (8). Thus, for X rays with an energy E and an RBE denoted by RBE(E),

\[ D_0(E) = \frac{7.2}{RBE(E)} \]

(3)

Thus Eq. (2) gives

\[ Y(E) = \frac{2.3 \times RBE(E)}{7.2} \]

(4)

In the core picture of lethality, the mean lethal efficiency \( \varepsilon(E) \) of core events produced by X rays of energy E is defined through the relationship

\[ Y(E) = Y_A(E) \times \varepsilon(E) \]

(5)

Thus

\[ \varepsilon(E) = \frac{Y(E)}{Y_A(E)} \times \frac{2.3 \times RBE(E)}{7.2 \times Y_A(E)} \]

(6)
Values of \( Y_d(E) \) have been calculated as described in our previous publication (4), and references for available experimental data on RBE are presented in Table 1 along with \( \varepsilon(E) \).

It is useful to represent \( \varepsilon(E) \) in terms of \( \varepsilon(E = 278 \text{ eV}) \), a value that has been measured many times (Table 1). It should be noted that this energy is just below the threshold energy of 290 eV for the carbon K shell and thus the core ionizations are only the L-shell ionizations of phosphorus atoms. One can then write the following expression:

\[
\varepsilon(E) = \frac{\varepsilon(278) \times \text{RBE}(E) \times Y_d(278)}{Y_d(E)}. \tag{7}
\]

Equation (7) is a more desirable way of evaluating the lethal efficiencies of core events because it is represented in terms of the ratio of the RBE values rather than the absolute values of RBE.

Note that when the X-ray energy is equal or greater than 1500 eV, core ionizations occur not only as a result of direct photo-ionizations but also from atomic interactions of the secondary electrons, a phenomenon that requires a threshold energy of about twice the K-shell binding energy (9). These secondary core events are more complex than the primary events since they associate four ionizing particles: the projectile electron, before and after ionization, and the secondary and Auger electrons. Let \( E_i, E_j, E_k, \) and \( E_l \) represent the energies of these particles where \( i, j, k, \) and \( l \) denote any one of the four electrons in an arbitrary order; the corresponding lethal efficiency of these events, \( \varepsilon_i(E_i, E_j, E_k, E_l) \), may be calculated with one of the two following approximations (4):

1. A single electron is sufficient to create the kind of complex damage that leads to cell inactivation. The \( \varepsilon_i \) efficiency is then just the sum of the efficiencies of the various electrons, considered either individually or in pairs. Only pair configurations can be investigated experimentally since core events involving a single electron would be produced by X rays just above the carbon, nitrogen and oxygen thresholds and these particles would be so completely absorbed in biological matter that they would hardly penetrate the cell cytoplasm (4). Thus the following expression is used:

\[
\varepsilon_i(E_i, E_j, E_k, E_l) = \varepsilon(E_i, E_j) + \varepsilon(E_k, E_l). \tag{8}
\]

2. The production of complex lethal damage requires the participation of two electrons. Then the various electron pairs must be considered, and the following expression is used:

\[
\varepsilon_{ij}(E_i, E_j, E_k, E_l) = \varepsilon(E_i, E_j) + \varepsilon(E_k, E_l) + \varepsilon(E_i, E_l) + \varepsilon(E_j, E_k). \tag{9}
\]

We use Eq. (10) as a first approximation:

\[
\varepsilon_i = \frac{1}{2}(\varepsilon_{i1} + \varepsilon_{i2}). \tag{10}
\]

For X rays of various energies, the probability of secondary core events may be found in ref. (10). After correction from their contribution to RBE (1500) (Eq. 10), the lethal efficiency of the usual (500, 1000) core event (for which the 1000 eV secondary electron has not produced a secondary core ionization) is found to be \(-1.7\%\). Lethal efficiencies deduced from available experimental data are presented in Table 1.
assumption at 2153 eV. This means that the contribution of interactions other than core events on DNA to lethality is small. This conclusion should be even more true for ultrasoft X rays with energies above the carbon and oxygen K-shell thresholds when the proportion of core interactions on DNA is of the order of 90%.

Evaluation of Contribution of Core Event to Cell Inactivation by Low-LET Radiation

Conceptually, the phenomena of core events are relatively simple to understand for ultrasoft X rays. For standard ionizing radiations such as high-energy electrons and γ rays, it is somewhat complex because of the presence of many events besides core events. Outer-shell excitation and ionization phenomena have large cross sections, and they are present simultaneously with the core events. Experimentally it is difficult to separate them, and hence one must rely on theoretical models to evaluate the importance of core events. We now proceed to calculate the contribution of core events (αK contribution) to cell inactivation for low-LET radiation. Typical examples of such radiation qualities are 100 keV electrons and γ rays.

For such radiation quality we will define the «K» contribution to the cell inactivation (CK) as the ratio between the theoretical value of the number of lethal events per gray due to the core events only and the experimental determined total number of lethal events per gray due to all the processes of ionization and excitation and the core events.

For 100 keV electrons, based on Eq. (4) and an average RBE of 0.9 for V79 cells (21, 22), the yield of experimental lethal events is Yexp = 0.28. The mean number of lethal events per gray coming from core events on DNA can only be expressed by

\[
Y_{k, exp} = \sum_i Y_k \times \langle \varepsilon_{k,i}(E) \rangle,
\]

where \( Y_k \) is the number of core events per gray for the species \( i \) and \( \langle \varepsilon_{k,i}(E) \rangle \) is the mean lethal efficiency relative to core events of species \( i \). (We call the lethal efficiency of an event its probability to lead to cell death.)

We have for the «K» contribution to the lethality

\[
C_k = \frac{Y_{k, exp}}{Y_{k, theo}} = \frac{\sum_i Y_k \times \langle \varepsilon_{k,i}(E) \rangle}{0.28}.
\]

Theoretical evaluations of \( Y_k \) and \( \langle \varepsilon_{k,i}(E) \rangle \) are explained below.

1. Number of core events on the DNA per gray

We simulated by Monte Carlo technique the interactions produced by the track of a radiation in a homogeneous environment. The purpose of our calculation is to evaluate the mean number of core events created by 1 Gy of 100 keV electrons in liquid water. We then deduce the number of core events in the DNA by a proportionality factor taking to account the atoms involved and the extent to which they can be ionized in their inner shells. The calculation is performed for a collection of cells irradiated at electron equilibrium involving secondary electrons.

According to Eq. (12), 1 Gy of 100 keV electrons corresponds to the full absorption of \( Y(E_{100 \text{keV}}) = (289 \times 10^{-15})/(100 \times 1.6 \times 10^{-16}) = 18.1 \) primary electrons in a V79 cells nucleus.

In the following we call \( N_k \) the total number of core events produced along a 100 keV electron track in water. The yield \( Y_k \) of core events on DNA per gray of 100 keV electrons absorbed in the nucleus is extracted from the number \( Y_k(E_{100 \text{keV}}) \times N_k \) of core events produced by the 100 keV electrons in the nucleus-equivalent volume of water, corrected for the relative abundances of the atoms in the DNA and in the nucleus, weighted by the respective inner-shell ionization cross sections.

Let \( n_c, n_n, n_o, n_p, \) and \( n_s \) be the numbers of atoms of the various species in the DNA and \( N_{k,0} \), the number of water molecules in the nucleus-equivalent volume (see Table 2). The yield of core events on DNA per gray absorbed in cell is

\[
Y_k = Y_k(100 \text{keV}) \times N_k \times \left[ \frac{n_c \times \sigma_{c,i}(E) + n_n \times \sigma_{n,i}(E) + n_p \times \sigma_{p,i}(E) + n_s \times \sigma_{s,i}(E)}{N_{k,0} \times \sigma_{k,i}(E)} \right],
\]

where \( \sigma_{c,i}, \sigma_{n,i}, \sigma_{p,i}, \sigma_{s,i}, \) and \( \sigma_{k,i} \) are the cross sections for inner-shell ionizations of carbon, nitrogen, oxygen, phosphorus and sodium atoms by primary and secondary electrons with energy \( E \). Cross sections are given per two electrons. The contribution of phosphorus K-shell ionization is negligible. Also, the cross section for sodium L-shell ionization is not included since the L shell of sodium is not an inner shell and its excitation does not give rise to a core event. The above average is done over all the energies appearing in the slowing down of the primary particle and of the electrons of subsequent generations.

The calculation will be derived considering that the target is DNA alone without the first hydration layer. Indeed, events in this first layer participate in direct effects (26), but they have a low probability to yield double-strand breaks (27).

The number, \( Y_k \), of core event in the species \( i \) is equal to

\[
Y_k = Y_k(100 \text{keV}) \times N_k \times \frac{n_i}{N_{k,0}} \times \frac{\langle \varepsilon_{k,i}(E) \rangle}{\sigma_{k,i}(E)},
\]

We use Kim’s cross sections corrected for relativistic effects (28), which agree with experimental data within 5% uncertainty. The various ratios \( \sigma_{c,i}/\sigma_{k,i} \) of the cross sections in Eq. (15) have been determined in the linear decreasing part of the cross-section curves relative to the energy and are given in Table 3. The energy range where the cross-section curves are linear corresponds to the energy range of the emitted electrons in the interaction of 100 keV electrons with water molecules. Ratios are per electron pair and per shell. For phosphorus it is the L shell with eight electrons, explaining the factor of 8 in Eq. (15).

The values of \( N_k \) have been calculated by two different codes: TILDA for water vapor and TRACELE for liquid water.

The TILDA code has been described previously (29). For electron kinetic energies below 10 keV, it is now implemented with refined theoretical ionization cross sections (30), taking into account the projectile-electron and target-electron interactions in the entrance and exit channels, respectively. Doubly differential d\( \varepsilon \)d\( \theta \)d\( \delta \)d\( E \), as well as singly differential cross sections are calculated, and the latter cross sections compare well

### Table 2

<table>
<thead>
<tr>
<th>Element</th>
<th>Number of atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>( N_{h,0} = \frac{M_{\text{nucleic}}}{m_{H_2O}} \times 6.02 \times 10^{23} = 9.66 \times 10^{22} )</td>
</tr>
<tr>
<td>Carbon</td>
<td>( n_c = 1.11 \times 10^{14} )</td>
</tr>
<tr>
<td>Oxygen</td>
<td>( n_o = 7.82 \times 10^{14} )</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>( n_n = 3.88 \times 10^{14} )</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>( n_p = 1.04 \times 10^{14} )</td>
</tr>
<tr>
<td>Sodium</td>
<td>( n_s = 0.57 \times 10^{14} )</td>
</tr>
</tbody>
</table>

### Table 3

| Average Ratios of Inner-Shell Cross Sections in Shell \( f \) (K or L) of the Atoms \( i \) of the DNA: \( \sigma_{i,f} \), Relative to the One in the K Shell of the Oxygen: \( \sigma_{O,K} \) |
|-----------------|-----------------|-----------------|-----------------|
| \( \frac{\sigma_{c,K}}{\sigma_{c,L}} \) | \( \frac{\sigma_{n,K}}{\sigma_{n,L}} \) | \( \frac{\sigma_{p,K}}{\sigma_{p,L}} \) | \( \frac{\sigma_{s,K}}{\sigma_{s,L}} \) |
| 2.0             | 1.5             | 4.2             | 1.0             |
with experimental data. For high-energy electrons, Kim’s cross sections corrected for relativistic effects (28) have been used.

The TRACELE code is derived for liquid water and is described in details in ref. (31). Ionization cross sections are those of Rudd (32) adapted for the liquid phase and are used for electrons up to 150 keV.

Table 4 presents the results of the two codes in calculating the number of core events created by a 100 keV electron along its path. Core events created by the primary and secondary electrons are distinguished here since their local ionization densities are not the same so that different lethal efficiencies must be associated with them.

These codes also make it possible to calculate the average potential of ion-pair production \( W_0 \) for various energies. The results obtained for an electron of 100 keV are in agreement with the data in the literature, which confirms the reliability of these codes.

Table 5 presents the various yields of core events on the DNA per gray of 100 keV electrons as indicated in Eq. (16) based on the TILDA and TRACELE codes.

2. Calculation of the mean lethal efficiencies of the core events created by 100 keV electrons along their pathways

The structure of the core events produced by fast electrons is represented by the diagram of Fig. 1. Whereas the Auger electrons have well-defined energies (see Fig. 1), the secondary electrons have a continuous probability distribution approximately proportional to \( 1/E_s^2 \) given by the theory of Kim (28).

The mean lethal efficiency for core events in the species \( i \) is given by

\[
\langle \epsilon_{\text{le}t} \rangle = \frac{1}{E_s} \int \frac{d\sigma}{dE_s} dE_s, \quad \langle \epsilon_{\text{le}t} \rangle = \frac{1}{E_s} \int \frac{d\sigma}{dE_s} dE_s, \quad \text{Eq. (17)}
\]

where \( d\sigma/dE_s \) is Kim’s differential cross section for the mean initial electron energy.

In this formula the efficiencies \( \epsilon(E_i, E_s) \) are the one displayed in Fig. 2. The experimental values in Fig. 2 represent the lethal efficiencies measured for core event created with ultrasoft X rays. They are extracted from the experimental RBE and from the number of core events on dry DNA in a way similar to that detailed in refs. (4) and (6), and their values are reported in Table 1. It is impossible to measure other experimental values because at the energy required, the photons would be too much attenuated in the cytoplasm to reach the nucleus. Thus the values used here are calculated and extrapolated from correspondence with available experimental values.

Table 6 summarizes the various mean lethal efficiencies of core events in the various atoms of the DNA. A fraction of core events, those created by low-energy electrons (about 3% according to the Monte Carlo simulation), are more complex. This is the case of core events of the second generation and those produced along the primary electron track end, which have a greater ionizing power. The Monte Carlo code provides the energy of the incident electron before and after the core ionization. So the complex core events (involving a four-electron pattern) are well determined and their lethal efficiency can be calculated according to the method described above. The consideration of these complex events increases the overall efficiency by \( \sim 7\% \).

RESULTS AND DISCUSSION

Comparison of the Lethal Efficiencies of Core Events Occurring in DNA Atoms or in \( ^{125}I \) Atoms Incorporated in DNA

The lethal efficiency of the decay of DNA-incorporated \( ^{125}I \) has been studied extensively. For CHO cells with a radiosensitivity close to that of V79 cells a 1.2% efficiency was reported (33). For V79 cells a 1% lethal efficiency was found (23). Finally, 1% or 2% values were found according to whether cells are harvested 1 or 5 h after \( ^{125}I \) labeling (34).

The energy deposition accompanying \( ^{125}I \) decay was studied by Pomplun et al. (35). They found that the total energy deposited in a volume 20 nm in diameter is 2.03 keV as a result of multiple ionizations (1.07 keV) and energy deposition by the Auger electrons (0.96 keV). The same quantity for core events in DNA would vary between 400 eV and 800 eV (Table 6).

However, when core ionization comes from \( ^{125}I \) decay, multiple charges take place in bases since the iodine atom is in the methyl position of thymidine so the coulombic effect and charge neutralization may lead to (likely complex) strand breaks.

By contrast, only two electrons in the harmful 200–500 eV range (see Fig. 2) are emitted in oxygen core ionizations instead of \( \sim 3.6 \) (35) in \( ^{125}I \) decay.

Thus the larger lethal efficiency of oxygen core events compared to \( ^{125}I \) could indicate that the stronger effect of

![FIG. 1. Scheme of the structure of the core events produced by fast electrons. \( \epsilon_{\text{Auger}} \) energy of the Auger electrons. \( \epsilon_{\text{secondary}} \) energy of the secondary electrons.](Image 130x250)

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**Table 4**

Number of Core Events Created by a 100 keV Electron along its Path

<table>
<thead>
<tr>
<th>Code</th>
<th>( N_{k} )</th>
<th>( N_{k,\text{primary}} )</th>
<th>( N_{k,\text{secondary}} )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TILDA (29)</td>
<td>8</td>
<td>7.6</td>
<td>0.4</td>
<td>Present work</td>
</tr>
<tr>
<td>TRACELE (31)</td>
<td>9.4</td>
<td>8.5</td>
<td>0.9</td>
<td>(31)</td>
</tr>
</tbody>
</table>

**Table 5**

Various Yields of Core Events on the DNA per Gray of 100 keV Electrons

<table>
<thead>
<tr>
<th>Code</th>
<th>( Y_{k}^{t} )</th>
<th>( Y_{k}^{p} )</th>
<th>( Y_{k}^{p} )</th>
<th>( Y_{k}^{t} )</th>
<th>( Y_{k}^{d} )</th>
<th>( Y_{k}^{d} )</th>
<th>( Y_{k} )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TILDA (29)</td>
<td>3.4</td>
<td>0.9</td>
<td>1.2</td>
<td>2.6</td>
<td>0.05</td>
<td>0.10</td>
<td>8.1</td>
<td>Present work</td>
</tr>
<tr>
<td>TRACELE (31)</td>
<td>4.0</td>
<td>1.1</td>
<td>1.4</td>
<td>3.0</td>
<td>~0</td>
<td>~0</td>
<td>9.5</td>
<td>Present work</td>
</tr>
</tbody>
</table>
the multiple charges in situ overcomes the lower one of the electrons. It could also be that the large ionization density due to low-energy electrons accompanying $^{125}$I decay reduces the indirect effect.

**Contribution of Core Events to Cell Inactivation by Low-LET Radiations**

Table 7 gives the values of $Y_{lethal}$ calculated for 100 keV electrons and for 1 MeV photons from Eq. (13). Experimental $Y_{lethal}$ extracted from Eq. (4) are also presented (with RBE = 1 for $^{60}$Co γ rays and RBE = 0.88 for 100 keV electrons). This last value is the average of the electron RBE at 20 keV [0.85 (21)] and the RBE at 1 MeV [0.91 (22)]. For 1 MeV photons, we use the number of core events on the DNA as reported in ref. (10).

It should be remembered that the contribution of core events to cell inactivation, defined as the ratio between the calculated and experimental $Y_{lethal}$, is given by $C_K = Y_{lethal}^{exp}/Y_{lethal}^{cal}$ (Eq. 14). For V79 cells the «K» contribution is of the order of 75%.

**Uncertainty on the Core Contribution to Cell Inactivation**

The main contribution to $Y_{lethal}$ (Eq. 13) is the one relative to the carbon atoms. The relative standard error on $Y_{K}$, due to the theoretical errors of the many cross sections used and to statistical errors, is $\sim$20%.

The relative standard error on $\langle e_{i0}^+(E) \rangle$, due to many uncertainties on the experimental points determining the shape and the height of the e curve in Fig. 2, is 30%.

Thus the relative standard error on $Y_{lethal}^{exp}$ is about 36%. Since the error on the 75% core contribution comes mainly from $Y_{lethal}^{exp}$, the relative error on this contribution is also of the order of 36%, and the absolute error is about 0.36 × 75% = 27%.

Finally, the «K» contribution to cell inactivation by usual (low-LET) radiation is found equal to $\sim$75 ± 27%.

**Core Model and Non-linear Effects**

The induction of core events is linear with dose, although survival curves typically have shoulders. A similar observation was also noted in the cluster model presented by Goodhead et al. (36) and was interpreted in terms of saturation of repair (37). The calculation presented here is based on a typical value of RBE at 10% survival (4). If the selected value of RBE at 1/e survival is used instead, there is no significant change in the core contribution.

**Core Ionization as a Potent Critical Event**

The main conclusion of this work is that the core contribution to the lethality of usual low-LET radiations such as fast electrons and γ rays is very large, of the order of 75%. It is interesting to note that we previously found a similar estimate for ions (4).

Originally the core model, in which the lethal effectiveness is associated only with core ionizations on DNA, was proposed for ultrasoft X rays. For these particles it is now demonstrated that this picture is basically correct since it not only qualitatively reproduces the RBE variations, especially the abrupt rise above compared to below the carbon K-shell threshold, but it also provides absolute values of core efficiencies consistent with experimental data. This conclusion is not surprising since core ionization is the main interaction channel of ultrasoft X rays with DNA.

By contrast, the new result presented here for low-LET radiations is noteworthy because core ionization phenomena represent no more than 10% of the total energy deposited by these particles (the same is true for ions).

It should be noted that the core model provides a natural explanation for the observation of an RBE increase for X rays with decreasing energy (11). This phenomenon is not-

**TABLE 6**

<table>
<thead>
<tr>
<th>Type of ionization (i)</th>
<th>$E_i$: Energy of the Auger electrons (eV)</th>
<th>$E_s$: Mean energy of the secondary electrons (eV)</th>
<th>$\langle e_{i0}^+(E) \rangle$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>K shell of carbon</td>
<td>250</td>
<td>147</td>
<td>3.0%</td>
<td>Present work</td>
</tr>
<tr>
<td>K shell of nitrogen</td>
<td>360</td>
<td>205</td>
<td>2.4%</td>
<td>Present work</td>
</tr>
<tr>
<td>K shell of oxygen</td>
<td>500</td>
<td>273</td>
<td>1.7%</td>
<td>Present work</td>
</tr>
<tr>
<td>L shell of phosphorus</td>
<td>110</td>
<td>77</td>
<td>1.1%</td>
<td>Present work</td>
</tr>
</tbody>
</table>
ing but a consequence of their increasing effectiveness to trigger core events.

The critical events leading to cell inactivation have been investigated for a long time. In previous stochastic models, clusters of ionizations produced at the track ends of low-energy electrons were thought to be the source of biological effects (36). These models are unable to reproduce the abrupt rise in RBE at the carbon K-shell threshold even when the specific atomic composition of DNA is considered (4). The present study shows that the lethal effect is predominantly associated with the pattern of two spatially correlated electrons and one positive hole, as achieved by core ionizations.

Moreover, there are some indications that these events could also be deeply involved in the production of chromosomal aberrations. Indeed, the RBE for chromosomal aberrations, like the one for cell inactivation, increases by a factor of about two for X rays above and below the carbon K-shell threshold (15, 38). This enhancement reproduces the one of core ionizations on DNA (4).

Therefore, the study of the various end points initiated by core ionizations on DNA appears to be an essential approach to characterize the nature of the critical radiobiological damage and the involved repair mechanisms.

Using ultrasoft X rays, the core events will allow a completely new way to view the fundamentals of radiobiological effects.

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