Published in final edited form as:

Radiat Res. 1993 April ; 134(1): 71–78.

On the Equivalent Dose for Auger Electron Emitters

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Abstract

Radionuclides that emit Auger electrons are widely used in nuclear medicine (e.g., ^{99m}Tc , ^{123}I , ^{201}Tl) and biomedical research (e.g., ^{51}Cr , ^{125}I), and they are present in the environment (e.g., ^{40}K , ^{55}Fe). Depending on the subcellular distribution of the radionuclide, the biological effects caused by tissue-incorporated Auger emitters can be as severe as those from high-LET α particles. However, the recently adopted recommendations of the International Commission on Radiological Protection (ICRP) provide no guidance with regard to calculating the equivalent dose for these radionuclides. The present work, using spermatogenesis in mouse testis as the experimental model, shows that the lethality of the prolific Auger emitter ^{125}I is linearly dependent on the fraction of the radioactivity in the organ that is bound to DNA. This suggests that the equivalent dose for Auger emitters may have a similar linear dependence. Accordingly, a formalism for calculating the equivalent dose for Auger emitters is advanced within the ICRP framework.

INTRODUCTION

Calculation of the absorbed dose and equivalent dose to tissues from incorporated radionuclides is important for risk assessment. Many radionuclides that decay by electron capture and/or internal conversion are widely used in diagnostic nuclear medicine (e.g., ^{99m}Tc , ^{111}In , ^{123}I , ^{201}Tl) and biomedical research (e.g., ^{51}Cr , ^{125}I). Others are present in the environment (e.g., ^{40}K , ^{55}Fe). These radionuclides are also finding a role in the treatment of cancer (1, 2). The electron capture and internal conversion modes of decay create an inner atomic shell vacancy which initiates a complex cascade of atomic de-excitation processes whereby numerous very low-energy electrons are emitted within $\sim 10^{-15}$ s (3). Most of these electrons, collectively known as Auger electrons, have energies ranging from a few to several hundred electron volts and correspondingly short ranges in tissue (several nanometers) (3). The dense shower of Auger electrons that are emitted by the radionuclide deposits energy in the immediate vicinity of the decay site, resulting in local energy densities that can exceed those along the tracks of densely ionizing α particles (4).

There is now a wealth of information from *in vitro* and *in vivo* studies concerning the radiotoxicity of Auger electron emitters (5–20). All of these experimental data show a striking dependence of the cytotoxicity on the subcellular distribution as might be expected given the highly localized energy deposition around the decay site (4). More specifically, when Auger emitters are situated outside the cell, or in the cytoplasm of the cell, only effects akin to radiations of low linear energy transfer (LET) are observed (6, 10, 17, 18, 20, 21) with values of relative biological effectiveness (RBE) of approximately one. In contrast,

localization of these radionuclides within the DNA in the cell nucleus can produce extreme radiotoxicity (RBE ~ 7–9 for cell killing) (5, 7, 9, 16–19). In fact, recent *in vivo* (16) and *in vitro* (7) studies have shown that the intense Auger cascades from DNA-incorporated ^{125}I are at least as lethal as 5.3 MeV α particles from intracellularly localized ^{210}Po . Furthermore, there is considerable experimental evidence to suggest that DNA binding of Auger emitters is not necessary to produce RBE values significantly greater than one. For example, when the Auger emitter ^{111}In is localized in the cell nucleus via the radiochemical ^{111}In -oxine, RBE values as high as 4 were observed *in vivo* (15) despite the fact that the radionuclide did not bind to DNA. Similar observations were made *in vitro* with ^{111}In -oxine (22, 23) and with ^{125}I -iodoantipyrene (24). In this context, it is also interesting to note that *trans*-dichlorodiammine- $^{195\text{m}}\text{Pt}$, which binds to DNA only partially (11),¹ and the DNA intercalating radiochemical ^{125}I -iodoproflavine (12) also yield RBE values of about 4–5. Thus all the available *in vivo* and *in vitro* experimental evidence clearly points out that the biological effects of Auger emitters can be severe depending on their subcellular localization, thereby warranting a closer look at the methods presently used to assess the risk from these radionuclides.

It has been common practice to use the dose equivalent, as defined by the International Commission on Radiological Protection (ICRP), to predict the risk associated with radiation exposure. In their earlier recommendations, the ICRP (25) defined the dose equivalent H according to the relationship $H = DQN$, where D is the absorbed dose, Q the quality factor, and N the product of all other modifying factors (e.g., dose rate). They also recommended $N = 1$ for all situations and $Q = 1$ for all electrons. Accordingly, application of these recommendations to Auger electron emitters would lead to a dose equivalent that is simply equal to the absorbed dose. The extreme radiotoxicity observed for a variety of Auger emitters, as noted above, is not accounted for by this approach. Recently, the ICRP updated their recommendations and newly defined the tissue equivalent dose $H_T = w_R D_{T,R}$, where w_R is the radiation weighting factor and $D_{T,R}$ is the absorbed dose to tissue T (26). No guidance is provided regarding radiation weighting factors for Auger emitters. In alluding to this problem, it was only indicated that microdosimetry techniques are required to establish w_R for Auger emitters. It should be noted, however, that until the radiosensitive targets within the cell nucleus are well defined and both the microscopic distribution of the radionuclide relative to the targets and the time dependence of the distribution are known, it is unlikely that meaningful microdosimetry calculations can be performed that predict the extremely varied biological effects caused by Auger emitters. Any microdosimetric approach is further complicated by the fact that RBE values are highly dependent on the model and the end point used. In as much as the ICRP (26) recommends that w_R values be based primarily on experimental RBE values, a coherent treatment of the equivalent dose for internal Auger emitters can be developed (based on existing data) in a phenomenological manner. Such an approach must account for the dependence of the toxicity of Auger emitters on their subcellular distribution.

In the present work, the radiotoxicity of the prolific Auger emitter ^{125}I was investigated as a function of its subcellular distribution using spermatogenesis in mouse testes as the experimental model. The subcellular distribution was varied by administering mixtures of two radiochemicals that target the cytoplasm ($\text{H}^{125}\text{IPDM}$) and nuclear DNA (^{125}IdU) of the testicular cells, respectively. The resulting RBE values are directly proportional to the fraction of testicular activity that is incorporated into the DNA of the testicular cells. Based on these data, an expression for the equivalent dose from incorporated Auger emitters that accounts for the subcellular distribution is advanced within the ICRP framework.

¹R. W. Howell, *Radiobiological Effects of Auger Electrons in the Decay of Pt-195 m*. Ph.D. Dissertation, University of Massachusetts, Amherst, 1987.

MATERIALS AND METHODS

Biological Model

Spermatogenesis in the mouse testis is used as the experimental model in this study with spermhead survival serving as the biological end point. This highly sensitive model, which is also relevant to humans (27, 28), has been used extensively to study the biological effects of external radiation (27, 29, 30) and incorporated radionuclides (13–18, 31). The testis contains several different cell populations. Of these, the spermatogonial cells (types A₁–A₄, In, B) are the most radiosensitive with an LD₅₀ ~ 0.40 Gy in mice, whereas the other cell populations are substantially less radiosensitive (LD₅₀ ranging from 2.0 to 600 Gy) (32). Because of this differential radiosensitivity, initial radiation damage to spermatogonia, even at low doses, results in a reduced spermhead population when assayed 29 days after irradiation, the time required for the spermatogonia to become spermatids in stages 12–16 (13, 14, 17, 27, 29, 30).

General Procedures

Details of the experimental procedures were discussed previously (13, 15, 17, 20, 33). Briefly, the right testis of anesthetized Swiss Webster mice (8 to 9 weeks old, Taconic Farms, Germantown, NY) were injected with standard 3- μ l volumes containing the radiochemical. This intratesticular mode of administration facilitates clear delineation of the biological effects of low-energy Auger electrons without significant interference from penetrating low-LET radiations (γ , X rays) that is inherent in other modes of administration (i.e., intravenous, intraperitoneal) (13, 16, 33). The biological clearance of the radiochemicals was determined by injecting each of 40 animals intratesticularly with the same amount of radioactivity. Animals were sacrificed in groups of four by an overdose of anesthetic at various times after injection, the activity in the testis was determined using an NaI well counter, and the fraction of injected radioactivity remaining in the testis was determined. These data on biological clearance are needed to obtain the absorbed dose to the testis (see Results). The optimal day to perform the spermhead survival assay is when the spermhead count reaches a minimum. This day was established by injecting 40 mice intratesticularly with a fixed amount of activity and, on various days after injection, the animals were sacrificed in groups of four. The spermhead count was obtained by placing the testis in 1 ml deionized water, homogenizing, sonicating, and counting the sonication-resistant spermheads in a hemocytometer. For both the ¹²⁵I radiochemicals, the spermhead count attained its minimum on the 29th day after injection. This is the optimal day for the spermhead survival assay (16, 17). To determine the spermhead survival fraction as a function of the testicular absorbed dose, animals (in groups of four) were injected intratesticularly with various concentrations of the radiochemical and sacrificed on the optimal day, and the testicular spermhead counts were determined. The surviving fraction is the ratio of spermhead counts in the test group to the number of counts in the controls (injected with saline and/or unlabeled pharmaceutical). Subcellular distribution of the radiochemicals in the testicular cells was determined using the cell fractionation methods described in our earlier reports (13, 15, 17, 20, 33).

Radiochemicals

Two radiochemicals, having very different patterns of subcellular distribution in the testicular cells, were selected for these studies. The first radiochemical, ¹²⁵Iododeoxyuridine (¹²⁵IdU), obtained from ICN Radiochemicals (Irvine, CA), localizes almost entirely in the cell nucleus of the testicular cells and covalently binds to the DNA (16). Conversely, the second agent, H¹²⁵IPDM (*N,N,N'*-trimethyl-*N'*-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propanediamine) (34), localizes in the cytoplasm of the testicular cells (17). Hence, using

mixtures of these two radiocompounds, the subcellular distribution of ^{125}I may be varied by changing the relative amounts of $\text{H}^{125}\text{IPDM}$ and ^{125}IdU administered.

Mixtures of ^{125}I -Labeled Radiochemicals

We reported earlier (16, 17) that intratesticular administration of $\text{H}^{125}\text{IPDM}$ (cytoplasmic localization) produces biological effects akin to low-LET radiation with an $\text{RBE} = 1$ compared to selective testicular irradiation with acute external X rays or chronic internal irradiation with the pure γ ray emitter ^7Be (15, 20, 33). In contrast, ^{125}IdU binds to DNA in the cell nucleus and produces the type of effects associated with high-LET radiation ($\text{RBE} = 7.9$) (16, 17). To vary the subcellular distribution of the radioactivity in a controlled manner, the radiochemicals ^{125}IdU and $\text{H}^{125}\text{IPDM}$ were administered sequentially to the animals. Thus the fraction of testicular activity bound to DNA was varied between 0 and close to 100%. A 4-h interval was allowed between the injections to allow the unbound ^{125}IdU to clear from the testis (Fig. 1). To ensure that sequential injection of the radiochemicals did not influence the individual clearance patterns and subcellular distributions, ^{125}IdU and $\text{H}^{131}\text{IPDM}$ were administered and the clearance of each was monitored separately (Fig. 1). $\text{H}^{131}\text{IPDM}$ was used because its 360 keV γ rays can be detected with an NaI well counter without interference from the ^{125}I -characteristic photons. The biological clearance and subcellular distribution of $\text{H}^{131}\text{IPDM}$ were identical to those of $\text{H}^{125}\text{IPDM}$ (20). These studies showed that the clearance and subcellular distribution of these radiochemicals were not influenced by the presence of the other as shown in Fig. 1. Therefore, the values of absorbed dose to the testis per megabecquerel of injected activity we reported previously (17) were used (0.30 Gy/MBq for ^{125}IdU and 2.82 Gy/MBq for $\text{H}^{125}\text{IPDM}$) to determine the testicular dose. To determine the dependence of spermhead survival on subcellular distribution of ^{125}I , the relative quantities of ^{125}IdU versus $\text{H}^{125}\text{IPDM}$ were varied and dose-response curves established for each mixture of the radiochemicals. The following combinations (activity ^{125}IdU activity $\text{H}^{125}\text{IPDM}$) were used: Mixture 1 (1:1.17), Mixture 2 (1:0.28), Mixture 3 (1:0.10). The dose-response curves for the individual radiochemicals were reported earlier (17, 20).

RESULTS

Figure 2 shows the spermhead survival as a function of the average testicular absorbed dose for the various radiochemical combinations. A least-squares fit of the data to a two-component exponential equation yields:

$$S(\text{Mixture 1}) = 0.32e^{-D/0.0041} + 0.68e^{-D/0.53}, \quad (1)$$

$$S(\text{Mixture 2}) = 0.34e^{-D/0.0097} + 0.66e^{-D/0.37}, \quad (2)$$

$$S(\text{Mixture 3}) = 0.45e^{-D/0.0037} + 0.55e^{-D/0.33}, \quad (3)$$

where D is the average absorbed dose (Gy) to the testis. Similar fits were obtained earlier for ^{125}IdU (16) and $\text{H}^{125}\text{IPDM}$ (17). The curve fits for the above combinations are also compared to the pure compounds in Fig. 2. As given in Table I, the mean lethal doses (D_{37}) are 0.68 ± 0.06 (17), 0.32 ± 0.04 , 0.21 ± 0.03 , 0.13 ± 0.01 , and 0.085 ± 0.021 Gy (16) for $\text{H}^{125}\text{IPDM}$, Mixture 1, Mixture 2, Mixture 3, and ^{125}IdU , respectively. Selective external irradiation of the mouse testes with acute 60 or 120 kVp X rays yielded a D_{37} of 0.67 ± 0.03 Gy (15). Accordingly, when compared to external X rays, the values of relative biological effectiveness at D_{37} are 2.1, 3.1, and 5.2 for Mixture 1, Mixture 2, and Mixture 3, respectively (Table I).

The two-component nature of the survival curves shown in Fig. 2 is characteristic of our model (13–17). It is most likely due to the differential radiosensitivity of the different types of spermatogonial cells (33). Similar two-component curves were also observed by Gasinska (35), Spano *et al* (36), and Oakberg (37).

Of particular importance to this work is the subcellular distribution of the radiochemicals. These data are summarized in Table I. The fraction of the radioactivity in the organ (cellular plus extracellular) that was associated with DNA in the testicular cell nuclei was 0, 0.063, 0.16, 0.42, and 0.84 for H¹²⁵IPDM, Mixture 1, Mixture 2, Mixture 3, and ¹²⁵I_D, respectively.

DISCUSSION

In the 1977 Recommendations of the ICRP (25) all electrons, including radionuclide emissions such as β rays and Auger electrons, were considered to be equally radiotoxic and were assigned a quality factor equal to one. However, in the years that followed the publication of the recommendations, it became increasingly clear that the cytotoxicity of the Auger emitter ¹²⁵I was more severe than expected when the radionuclide was bound to DNA in the cell nucleus (5, 6, 9, 38). In contrast, its effects were akin to low-LET sources of radiation when localized outside the nucleus (10). These considerations, in conjunction with transformation–mutation–aberration data for ¹²⁵I in the literature (39–43), led Pomplun *et al* (44) to propose a quality factor Q for ¹²⁵I that would reflect the radiotoxicity on the basis of its location within the cell. For the purposes of calculating the dose equivalent H , they (44) suggested that a quality factor of 1 should be used when ¹²⁵I is “outside the DNA,” whereas a quality factor equal to that for high-LET α particles would be appropriate when the radionuclide is localized “inside the DNA.” The recent data from *in vivo* (16) and *in vitro* (11) experiments which demonstrated that DNA-bound ¹²⁵I is as lethal as 5.3-MeV α particles from intracellularly incorporated ²¹⁰Po support their view that a quality factor similar to that of α particles may be appropriate. Such a recommendation should not be limited to ¹²⁵I since a number of other Auger emitters including ⁷⁷Br, ¹¹¹In, and ¹²³I exhibit comparable cytotoxic effects (8, 15, 45).

Although the above approach of Pomplun *et al* (44) is reasonable for simple situations where the intracellular distribution of radionuclides is distinct in that all of the radioactivity is either “inside the DNA” or “outside the DNA,” the distribution of the radionuclide in tissue is seldom this selective. In fact, the distribution of radiochemicals is typically complex, with radioactivity being found in the cytoplasm, nucleus, DNA, and extracellular spaces. Therefore, a more general approach is required to calculate the dose equivalent H for Auger emitters. Furthermore, the ICRP (26) dropped the use of H and Q recently and introduced the concept of the radiation weighting factor w_R and equivalent dose H_T . Hence any new approach should be developed within this new set of definitions.

The equivalent dose in an organ or tissue T is defined as $H_T = w_R \cdot D_{T,R}$, where w_R is the radiation weighting factor and $D_{T,R}$ is the absorbed dose from radiation R . For a mixed radiation field such as those emitted by many radionuclides including Auger emitters,

$$H_T = \sum_R w_R \cdot D_{T,R} \quad (4)$$

The ICRP (26) assigned $w_R = 1$ for all electrons, with the exception of Auger electrons emitted by nuclides bound to DNA. No specific value for w_R was recommended for Auger electrons under these circumstances. If the collective action of the Auger electrons is ignored, and w_R is considered for each electron individually (i.e., $w_R = 1$), the equivalent

dose for ^{125}I would simply be $H_T = \Sigma D_R$. This approach clearly does not reflect the spectrum of observed RBE values for ^{125}I and suggests that a collective radiation weighting factor for Auger electrons w_{Auger} is necessary. In that event, the equivalent dose for DNA-bound Auger emitters may be written as

$$H_T = H_{T_{\text{Auger}}} + H_{T_{\text{other}}} \\ = w_{\text{Auger}} \cdot \sum_{R_{\text{Auger}}} D_{T,R_{\text{Auger}}} + \sum_{R_{\text{other}}} w_{R_{\text{other}}} \cdot D_{T,R_{\text{other}}} \quad (5)$$

In keeping with our previous report (7), further modification of Eq. (5) is required to accommodate the dependence of H_T on the subcellular distribution of the Auger electron emitter. The experimental data presented in this work may be useful in this regard. When the RBE values of the ^{125}I IdU/ ^{125}I IPDM mixtures are correlated with the fraction of the radioactivity in the organ bound to DNA (Table I), a linear relationship is observed (Fig. 3). A least-squares fit to the experimental data yields

$$\text{RBE} = 1.0 + (8.7 \pm 0.6)f_o, \quad (6)$$

where f_o is the fraction of the radioactivity in the organ bound to DNA. This finding is important in that, given the subcellular distribution of an Auger emitter, one can predict the biological response and therefore the RBE. Since the radiation weighting factor should be a reflection of experimental RBE values [Annex A, Item A9 in Ref. (26)], w_{Auger} may have a similar linear dependence on f_o . However, w_R is also based on the quality of the radiation [Annex A, Item A10 of Ref. (26)], which should be an inherent property of the radiation that does not depend on the decay site. Therefore, it is perhaps more appropriate to modify $H_{T_{\text{Auger}}}$ as required. With this in mind, the equivalent dose specifically for the Auger electrons may be expressed as

$$H_{T,R_{\text{Auger}}} = (1 + f_o(w_{\text{Auger}} - 1)) \sum_{R_{\text{Auger}}} D_{T,R_{\text{Auger}}} \quad (7)$$

This equation limits appropriately at $f_o = 0$ and $f_o = 1$ and is similar to the expression for the dose equivalent H suggested in our earlier report (7).

Although Eq. (7) is fundamentally sound, separating the biological effects of the Auger electrons from other radiations emitted by the radionuclide is not possible experimentally because the observed RBE values are for the composite spectrum of emissions. Therefore, it is difficult to assign a value to w_{Auger} that corresponds directly to measured RBE values. For example, consider the case of ^{125}I IdU in the testis. The various radiations emitted by ^{125}I are listed in Table II, the low-LET components being the conversion electrons, X rays, and γ rays. Of the absorbed dose received by the testis from ^{125}I decays (see Table II), 57% is delivered by the Auger electrons while 43% is from the remaining low-LET radiation components (RBE = 1). In principle, one may obtain the relative biological effectiveness for the Auger electrons $\text{RBE}_{\text{Auger}}$ by stripping off the absorbed-dose contributions of the low-LET radiation components. Hence $\text{RBE}_{\text{experimental}} = 0.57 \text{ RBE}_{\text{Auger}} + 0.43 \text{ RBE}_{\text{other}}$, where $\text{RBE}_{\text{other}} = 1$. At D_{37} , $\text{RBE}_{\text{experimental}} = 7.9$; therefore $\text{RBE}_{\text{Auger}} = 13$. A similar approach may be useful in determining w_{Auger} using models and end points that are more relevant to carcinogenesis.

In the discussion above it has been presumed that the biological damage caused by Auger emitters is due largely to radiation effects (direct + indirect) (17, 46, 47). Other mechanisms

have also been considered, including transmutation of the atom (i.e., $^{125}\text{I} \rightarrow \text{stable } ^{125}\text{Te}$) and charge neutralization (46, 48). However, even if these latter two mechanisms are in part responsible for the observed biological effects, $\text{RBE}_{\text{Auger}}$ takes all mechanisms into account in that it represents the overall observed biological effect. Therefore, the above expression for the equivalent dose for Auger emitters [Eq. (7)] is appropriate irrespective of the mechanisms responsible for the Auger effect.

So far our discussion has been limited to the prolific Auger emitter ^{125}I . By necessity, any method to calculate the equivalent dose for Auger emitters must be able to accommodate all such radionuclides. The *in vitro* data of Kassis *et al* (49) indicate that all Auger emitters may be equally radiotoxic when similarly bound to DNA in a covalent fashion. They found that, in spite of the differences in the average number of Auger electrons emitted per decay, the three Auger emitters ^{77}Br (7 per decay), ^{123}I (11 per decay), and ^{125}I (20 per decay) all yielded essentially the same RBE value (~ 7) for cell killing. These data suggest that w_{Auger} may be independent of the magnitude of the Auger cascades and should have the same value for all Auger emitters.

There remain additional concerns regarding calculation of the equivalent dose for Auger emitters. There is substantial experimental evidence that Auger emitters localized in the cell nucleus and not bound to DNA (15, 22–24), or noncovalently bound to the DNA (11, 12), are also extremely radiotoxic, albeit somewhat less severe than for those covalently bound to the DNA. In these instances RBE values of about 4 were observed for cell killing compared to 7–9 for covalently bound emitters (7, 9, 16). In principle, calculation of the equivalent dose could be modified to accommodate these circumstances by introducing an additional parameter. In the absence of a substantial database for this class of radiochemical, a simple, yet conservative, approach would be to calculate the equivalent dose in the same manner [Eq. (7)] regardless of where the radionuclide is localized in the nucleus.

There may also be cases where irradiation of tissue with internal Auger emitters may lead to experimental RBE values less than one. For example, consider the Auger emitter ^{51}Cr which has a small yield (0.11 per decay) of high-energy γ rays and no dosimetrically significant particulate radiation component that is able to penetrate more than $\sim 1 \mu\text{m}$. In this case, the majority of the energy deposited in small organs such as the mouse testis is from the nonpenetrating low-energy Auger electrons. When ^{51}Cr is predominantly localized extracellularly, or in the cytoplasm of the cells, very little energy is deposited in the cell nuclei which presumably contain the radiosensitive targets. Accordingly, the relative biological effectiveness compared to external X rays is expected to be less than one. This notion is supported by our recent data for intratesticularly administered $\text{Na}^{51}\text{CrO}_4$ which yielded an RBE value of ~ 0.3 (50). Of the ^{51}Cr in the testis, 81% of the activity was localized extracellularly while the remaining 19% was found within the testicular cells. About 15% of the intracellularly localized activity was in the nucleus and 85% in the cytoplasm. Similarly, $^{99\text{m}}\text{Tc}$ -pyrophosphate, with a localization of 60% extracellular/40% cellular and 32% nuclear/68% cytoplasmic, yielded an RBE value of ~ 0.8 . These results indicate that Eq. (7) is not universal for all Auger emitters in that there is no provision for the emitter to be less effective ($\text{RBE} < 1$) than the conventional reference radiation (i.e., external X rays). Such situations may be accommodated by introducing yet another parameter to account for RBE values less than one. However, for the purposes of radiation protection, it may be prudent to overestimate the risk for the time being by simply calculating the equivalent dose in the conventional manner.

Finally, it should be noted that the arguments above are based largely on survival data. It may be necessary to confirm Eq. (7) using end points more relevant to carcinogenesis. Such data are also important for establishing w_{Auger} because the RBE generally depends on the

biological end point. The existing *in vivo* (16) and *in vitro* (7) survival data, that show the radiotoxicity of DNA-bound ^{125}I is the same as that of 5.3 MeV α particles emitted by incorporated ^{210}Po , suggest that w_{Auger} may be at least as large as the value of w_R for α particles. However, this stance is tempered by the observation that the 5.3 MeV α particles are about four times more effective than DNA-bound ^{125}I in producing spermhead abnormalities (18). Therefore, in arriving at w_R , care should be exercised with respect to the biological model used as well as the end points for which the RBE is calculated (18, 33). In addition, dose-rate considerations may also be important (7, 18, 33).

In conclusion, the approach presented in this paper represents a practical first step toward the estimation of equivalent dose for incorporated Auger electron emitters, an aspect that has not been given adequate consideration so far. Given the widespread use of this class of radionuclides in nuclear medicine and biomedical research, the formalism presented here may be of value in assessing the risk associated with exposure to these radionuclides as well as predicting their therapeutic efficacy.

Acknowledgments

The chemical HIPDM was kindly provided by Professor Hank Kung (University of Pennsylvania, Philadelphia, PA). This work was supported in part by USPHS Grant CA-32877 (DVR) and New Jersey Cancer Commission Fellowship 689-082 (VRN).

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FIG. 1.

Biological clearance of ^{125}IdU (●) and $\text{H}^{131}\text{IPDM}$ (▲) following their sequential injection into mouse testis. The 360 keV γ rays from ^{131}I and the characteristic photons from ^{125}I were followed independently using an NaI well counter. The biological clearance patterns were essentially identical to those observed in our previous reports (16, 17) for $\text{H}^{125}\text{IPDM}$ (Δ) and ^{125}IdU ($\circ$) alone. Hence their individual clearance patterns were not influenced by the presence of the other. These data represent the average of two experiments for each case. Standard deviations of the mean fall within the spatial dimensions of the data points.

FIG. 2.

Spermhead survival in mouse testis following sequential intratesticular administration of ^{125}IdU and $\text{H}^{125}\text{IPDM}$. The radiochemical ^{125}IdU localized in the DNA of the testicular cell nuclei while $\text{H}^{125}\text{IPDM}$ resided in the cytoplasm. The fraction of testicular radioactivity bound to DNA in the cell nuclei was varied by altering the relative amounts of the injected radiochemicals (activity ^{125}IdU :activity $\text{H}^{125}\text{IPDM}$, symbol): Mixture 1 (1:1.17, □), Mixture 2 (1:0.28, ▽), Mixture 3 (1:0.1, ◇). The survival curves for ^{125}IdU (16) and $\text{H}^{125}\text{IPDM}$ (17) injected alone are given by the dotted and dashed lines, respectively. Error bars represent standard deviations of the mean.

FIG. 3. Dependence of the relative biological effectiveness (at D_{37}) of ^{125}I on the fraction f_o of testicular radioactivity bound to DNA. Standard deviations of the mean are indicated by the error bars.

TABLE IRelative Biological Effectiveness of Mixtures of ^{125}IdU and $\text{H}^{125}\text{IPDM}$

	Injection mixture (activity:activity) $^{125}\text{IdU}:\text{H}^{125}\text{IPDM}$	Fraction of radioactivity in the organ bound to DNA	D_{37} (Gy)	RBE ^a
$\text{H}^{125}\text{IPDM}$	0:1	0	0.68 ± 0.06	1.0 ± 0.1
Mixture 1	1:1.17	0.063	0.32 ± 0.04	2.1 ± 0.3
Mixture 2	1:0.28	0.16	0.21 ± 0.03	3.1 ± 0.4
Mixture 3	1:0.10	0.42	0.13 ± 0.01	5.2 ± 0.6
^{125}IdU	1:0	0.84	0.085 ± 0.02	7.9 ± 2.4

^aRBE compared to acute external X rays.

TABLE II

¹²⁵I Average Radiation Spectrum^a

	Average energy (MeV)	Yield/ decay	Percentage contribution to testicular dose
γ_1	3.55×10^{-2}	0.0647	0.3
K conversion e^-	3.65×10^{-3}	0.797	34.0
L conversion e^-	3.06×10^{-2}	0.110	
M, N conversion e^-	3.47×10^{-2}	0.0284	
$K_{\alpha 1}$ X ray	2.75×10^{-2}	0.751	8.7
$K_{\alpha 2}$ X ray	2.72×10^{-2}	0.394	
$K_{\beta 1}$ X ray	3.10×10^{-2}	0.138	
$K_{\beta 2}$ X ray	3.17×10^{-2}	0.0403	
$K_{\beta 3}$ X ray	3.09×10^{-2}	0.0685	
$K_{\beta 5}$ X ray	3.12×10^{-2}	0.0012	
KM, N, O X ray	3.17×10^{-2}	0.0030	
L X ray	3.93×10^{-3}	0.132	
M X ray	5.42×10^{-4}	0.0040	
KLL Auger e^-	2.24×10^{-2}	0.138	57.0
KLX Auger e^-	2.64×10^{-2}	0.0590	
KXY Auger e^-	3.02×10^{-2}	0.0065	
LLX Coster-Kronig e^-	2.19×10^{-4}	0.264	
LMM Auger e^-	3.05×10^{-3}	1.25	
LMX Auger e^-	3.67×10^{-3}	0.340	
LXY Auger e^-	4.34×10^{-3}	0.0211	
MMX Coster-Kronig e^-	1.27×10^{-4}	1.44	
MXY Auger e^-	4.61×10^{-4}	3.28	
NNX Coster-Kronig e^-	2.99×10^{-5}	3.51	
NXY Auger e^-	3.24×10^{-5}	10.9	
OOX Coster-Kronig e^-	6.00×10^{-6}	3.66	

^aTaken from Ref. (51).