ENGINEERING PHYSICS AND MATHEMATICS DIVISION

Mathematical Sciences Section

**MARROW CELL KINETICS MODEL:
EQUIVALENT PROMPT DOSE APPROXIMATIONS
FOR TWO SPECIAL CASES**

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ABSTRACT

Two simple algebraic expressions are described for approximating the “equivalent prompt dose” as defined in the model of Jones et al. (1991). These approximations apply to two specific radiation exposure patterns: (1) a pulsed dose immediately followed by a protracted exposure at relatively low, constant dose rate and (2) an exponentially decreasing exposure field.

INTRODUCTION

This document describes two approximations derived from the cell kinetics model presented and discussed by Jones et al. (1991) and Morris et al. (1991). That model was constructed to simulate processes of cell injury, killing, repair, and proliferation in a population of cells “critical” to myelopoiesis during and following radiation injury. The mathematical form is a set of differential equations that requires specification of five rate coefficients. The coefficient values used in this work are

$$\lambda_{NI} = 4.63 \times 10^{-3} \text{ cGy}^{-1} \text{ for radiation injury to normal cells}$$

$$\lambda_{IN} = 2.22 \times 10^{-2} \text{ min}^{-1} \text{ for repair of injured cells}$$

$$\lambda_{NK} = 1.45 \times 10^{-3} \text{ cGy}^{-1} \text{ for radiation killing of normal cells}$$

$$\lambda_{IK} = 3.23 \times 10^{-3} \text{ cGy}^{-1} \text{ for radiation killing of injured cells}$$

$$\lambda_{NN} = 8.26 \times 10^{-5} \text{ min}^{-1} \text{ for proliferation of normal cells.}$$

Additional biophysical interpretation of these quantities is given in the two references mentioned above. These particular values are estimates derived from a large collection of animal mortality data, and incorporate adjustments in λ_{NI} , λ_{NK} , and λ_{IK} for ^{60}Co radiation (relative to 250 kVp

X-rays) and in λ_{NI} and λ_{NK} for the amount of genetic material per cell nucleus for humans (vs mice).¹ We consider these coefficients to be our current best estimates for use in modeling of human exposure to ^{60}Co radiations.

The model can be used to calculate an "equivalent prompt dose" (EPD) for any short, fractionated, or protracted uniform whole-body exposure, where equivalency is relative to the size of the surviving population of critical cells. That is, for any specified exposure pattern, the model can be used to calculate the prompt (high rate) dose at which the same number of cells would survive. In the following, we describe approximations of equivalent prompt dose that are empirically determined from the model. The two specific radiation exposure patterns to which these approximations apply are (1) a pulsed dose immediately followed by a protracted exposure at relatively low, constant dose rate (Case 1) and (2) an exponentially decreasing exposure field (Case 2).

The approximations given here are empirically derived. The mathematical forms used were selected only for their ability to quantitatively mimic the cell kinetics model and are not intended to suggest the biological or biophysical processes involved in myelopoiesis. Also, the approximations should not be used outside of the range of parameter values given. The single exception to this range limitation is in Case 2, where equivalent prompt doses for exposures of duration greater than 2 d may be approximated as described.

In all algebraic expressions, "log(.)" denotes the natural logarithm of the argument, "max(..)" denotes the larger of the two arguments, and "min(..)" denotes the smaller of the two arguments.

1. Morris, M. D., T. D. Jones, and R. W. Young, 1992. "A cell kinetics model of radiation-induced myelopoiesis: rate coefficient estimates for mouse, rat, sheep, swine, dog, and burro irradiated by photons," manuscript submitted for journal review.

CASE 1

The exposure pattern is a “pulsed” or prompt dose, followed by a continuous protracted exposure at a relatively low, constant dose rate for a number of days. This case might correspond, for example, to initial radiation from a low-yield nuclear detonation followed by exposure to neutron-activated radiosotopes (Fig. 1). Let

D_1 = the prompt dose,

t = the length of time of the protracted exposure,

D'_2 = the dose rate of the protracted dose.

In what follows, t is given in days. The values of D_1 and D'_2 given in the following are in units of marrow centi-Gray and marrow centi-Gray per minute, respectively; however, the approximation holds for other units as explained in the following.

The range of parameter values used to construct the approximation is

$D_1 = 0$ through 300 cGy, in increments of 20 cGy;

$t = 1$ through 30 d, in increments of 1 d;

$D'_2 = 0.01$ through 0.1 marrow cGy/min, in increments of 0.01 marrow cGy/min.

Over this joint range of the three exposure parameters, the total (or integrated) dose ranges from 14.4 to 4620.0 cGy, with a mean of 1377.6 cGy and standard deviation of 1008.9 cGy. Because these are protracted exposures, the total doses are much larger than the corresponding equivalent prompt doses as calculated using the cell kinetics model. Equivalent prompt doses range from 13.2 to 783.0 cGy, with a mean of 352.1 cGy and standard deviation of 165.4 cGy.

Figure 1. Dose rate function for Case 1.

Approximation of Equivalent Prompt Dose for Given Time of Exposure

The suggested approximation to the equivalent prompt dose is

$$\text{EPD} = D_1 + \max(0, -0.148 \times D_1 + 1090 \times D'_2) \times \log(1 + t^2). \quad (1)$$

Accuracy of this approximation, evaluated over the grid of D_1 , t , and D'_2 indicated in the preceding, is summarized in Table 1. Overall root mean square error is 11.43 cGy. Quality of the approximation suffers most for small D_1 or large D'_2 when error is expressed in dose units. When proportional error is considered, approximations are least accurate for small D_1 or small D'_2 . However, of the 4800 points on the parameter grid, only 53 lead to approximation errors of 30 cGy or more, and at all but three of these points, this error is less than 10% of the corresponding equivalent prompt dose. Comparisons of modeled and approximate values of equivalent prompt dose are displayed in Fig. 2 for two combinations of D_1 and D'_2 .

As noted, this approximation is formulated using marrow centi-Gray for units of EPD and D_1 , and marrow centi-Gray per minute as units for D'_2 . However, any other dose or exposure units can be used in the equation as long as the transformation consists of multiplying each of EPD, D_1 , and D'_2 by a common fixed factor. (Both sides of the approximating equation are then multiplied by the same quantity; so, the relation continues to hold.) For example, D_1 and EPD are often converted to exposure units of free-in-air roentgen by dividing marrow dose by 0.71, and D'_2 is converted to free-in-air roentgen per minute by the same factor. Hence, the approximation holds for these units as well.

Table 1. Root mean square error of approximation for Case 1^a

D_1 (min)	RMSE ^b (cGy)	RMSPE ^c (%)	t (d)	RMSE (cGy)	RMSPE (%)	D'_2 (cGy/min)	RMSE (cGy)	RMSPE (%)
0	16.04	13.06	1-3	10.40	8.59	0.01	9.34	11.45
20	14.54	10.59	4-6	14.00	5.98	0.02	13.32	9.40
40	13.42	9.17	7-9	12.71	6.18	0.03	12.53	6.77
60	12.63	8.21	10-12	11.04	6.23	0.04	9.38	4.63
80	11.54	6.37	13-15	10.10	6.09	0.05	7.63	3.58
100	10.72	4.67	16-18	9.63	5.80	0.06	8.41	3.31
120	10.60	4.34	19-21	9.61	5.45	0.07	9.28	3.23
140	10.59	4.10	22-24	10.24	5.12	0.08	9.28	3.21
160	9.70	2.85	25-27	11.66	4.90	0.09	11.09	3.45
≥180	10.10	2.28	28-30	13.78	4.85	0.10	19.29	4.19

^aOverall, RMSE = 11.43 cGy, RMSPE = 6.01%.

^bRoot mean square error = $\sqrt{\text{av}[(\text{EPD}-\text{approximation})^2]}$.

^cRoot mean square percentage error = $\sqrt{\text{av}[(\text{EPD}-\text{approximation})^2/\text{EPD}^2]} \times 100\%$.

Figure 2. Comparison of model and approximation for two examples of Case 1.

Approximation of Time of Exposure for Given Equivalent Prompt Dose

Given D_1 between 0 and 300 cGy, and D'_2 between 0.01 and 0.10 cGy/min, Eq. (1) can be rearranged to yield an approximate time until a given equivalent prompt dose is realized. Hence, if a “permissible” (equivalent) prompt dose can be set, perhaps by consideration of human mortality estimates (e.g. Morris et al. 1989), a corresponding “permissible” time of exposure in a given field can be determined. The first step in this calculation is determination of the intermediate quantity

$$\beta = -0.148 \times D_1 + 1090 \times D'_2 .$$

If $\beta \leq 0$, this means that no equivalent prompt dose greater than D_1 will be attained, that is, that the protracted dose component is not contributing to equivalent prompt dose. (In these cases, repair and proliferation processes more than compensate for the slowly accumulating cell injury and for the occurrence of cell death in the protracted phase of exposure.) If $\beta > 0$, the time at which a given equivalent prompt dose is realized may be approximated as

$$t = \sqrt{e^{(EPD - D_1)/\beta} - 1} . \quad (2)$$

A value of t greater than 30 d represents an unreliable extrapolation beyond the parameter values used to construct this approximation. In such cases, t should be reported simply as > 30 d.

Examples

1. Approximate EPD for $D_1 = 40$ cGy, $D'_2 = 0.06$ cGy/min, and $t = 10$ d. Because

$$-0.148 \times D_1 + 1090 \times D'_2 = -0.148 \times 40 + 1090 \times 0.06 = 59.5$$

is greater than zero, equivalent prompt dose is approximated from Eq. (1) as

$$FPD = 40 + 59.5 \times \log(1 + 10^2) = 314.6 \text{ cGy} .$$

Had the first quantity calculated (i.e., 59.5) been negative, EPD would have been approximated as 40 cGy (i.e., D_1) for any t .

2. For $D_1 = 60$ cGy and $D'_2 = 0.04$ cGy/min, approximate the time at which EPD = 200 cGy. First, β is calculated as

$$\beta = -0.148 \times D_1 + 1090 \times D'_2 = -0.148 \times 60 + 1090 \times 0.04 = 34.7 .$$

This is greater than zero; so, using Eq. (2),

$$t = \sqrt{e^{(200-60)34.7} - 1} = 7.5 \text{ d} .$$

Had this value been greater than 30, the approximation would have been reported simply as > 30 d.

CASE 2

The exposure pattern is exponentially decreasing, where dose rate is proportional to elapsed time raised to the power -1.2. This function has been extensively used to represent a decaying fallout field (Fig. 3). [However, see Haaland (1987) for possible deficiencies in this representation.] Let

Δ = length of an initial period before exposure (or of total shielding),

t = length of time of exposure,

D' = dose rate at the beginning of the exposure.

Δ is given in minutes, and t in hours. Hence, dose rate is zero for an initial period of length Δ , and then is proportional to $(\Delta + \text{time} \times 60)^{-1.2}$ for any value of "time" up to t hours, with the proportionality constant set so that the dose rate at time Δ is D' . In this model, Δ must be greater

Figure 3. Dose rate function for Case 2.

than zero because $\Delta = 0$ corresponds to an infinite dose (i.e., nonintegrable dose rate over time). D' here is in units of centi-Gray per minute to marrow, but the approximation accommodates other common units of exposure or dose, as explained in the following.

The range of parameter values used to construct the approximation is as follows:

$\Delta = 3, 5, 10, 15, 20, 30, 45, 60, 90,$ and 120 min;

$t = 5/60$ through $55/60$ h (5 through 55 min), in increments of $5/60$ h (5 min);

1 through 23 h, in increments of 1 h;

24 through 48 h, in increments of 6 h;

$D' = 1$ through 10 marrow cGy/min, in increments of 1 cGy/min.

In comparison to the calculations made in Case 1, the times of exposure used here (t) are much more limited (up to 2 d vs 30 d in Case 1), since all combinations of Δ and D' examined produce little or no increase in equivalent prompt dose beyond $t = 48$ h. Over this joint range of the three exposure parameters, the total (integrated) dose ranges from 2.7 to 2848.2 cGy, with a mean of 335.0 cGy and standard deviation of 422.5 cGy. As in Case 1, the total doses are larger than the corresponding equivalent prompt doses, although the differences are not so great here because most of the dose is delivered in a relatively short period of time. Equivalent prompt doses range from 2.7 to 1667.8 cGy, with a mean of 240.3 cGy and standard deviation of 268.8 cGy.

Approximation of Equivalent Prompt Dose for Given Time of Exposure

The suggested approximation to the equivalent prompt dose is calculated as follows. First, if the desired value of t is greater than 48 h, replace it with $t = 48$. Then approximate equivalent prompt dose as

$$\log(\text{EPD}) = 1.43 + 0.775 \times \log(\Delta) - 0.0179 \times \log(\Delta) \times \log^2(t/48) + \log(D') ,$$

or equivalently,

$$\text{EPD} = 4.20 \times D' \times \Delta^{0.775 - 0.0179 \times \log^2(t/48)} \quad (3)$$

Accuracy of this approximation, evaluated over the grid of Δ , t , and D' indicated here, is summarized in Table 2. Overall root mean square error is 28.36 cGy. Quality of the approximation suffers most for large Δ , t , or D' when error is expressed in dose units, but small values of the parameters produce the greatest errors on a proportional scale. Of the 3900 points on the parameter grid, 329 lead to approximation errors of 50 cGy or more, but in each of these cases, the proportional error is less than 15% of equivalent prompt dose. Comparisons of modeled and approximate values of equivalent prompt dose are shown in Fig. 4 for two combinations of Δ and D' .

As in Case 1, units other than marrow centi-Gray and marrow centi-Gray per minute may be used for doses and dose rate, respectively, if the transformation can be accomplished by multiplying EPD and D' by a common constant factor.

Approximation of Time of Exposure for Given Equivalent Prompt Dose

Given Δ between 3 and 120 min and D' between 1 and 10 cGy/min, Eq. (3) can be rearranged to yield an approximate time until a given equivalent prompt dose is realized. First, calculate the intermediate quantity

$$\beta = 1.43 + 0.775 \times \log(\Delta) + \log(D') .$$

If $\beta \leq \log(\text{EPD})$, this means that the specified equivalent prompt dose will not be attained under the specified Δ and D' . If $\beta > \log(\text{EPD})$, the time at which the given equivalent prompt dose is realized may be approximated as

$$t = \min(48 \times e^{-7.47 \times \sqrt{(\beta - \log(\text{EPD})) / \log(\Delta)}}, 48) . \quad (4)$$

Table 2. Root mean square error of approximation for Case 2^a

Δ (min)	RMSE ^b (cGy)	RMSPE ^c (%)	t	RMSE (cGy)	RMSPE (%)	D' (cGy/min)	RMSE (cGy)	RMSPE (%)
3	5.45	15.72	5-20 min	6.33	17.26	1	6.13	11.98
5	4.14	8.27	25-40 min	12.26	11.11	2	7.07	9.86
10	7.15	8.49	45-60 min	16.53	11.49	3	11.58	9.17
15	10.69	9.72	2-5 h	24.53	9.06	4	17.53	9.00
20	13.24	10.00	6-9 h	30.93	7.02	5	23.24	8.99
30	16.40	9.32	10-13 h	34.23	6.49	6	28.37	9.06
60	19.41	7.48	14-17 h	35.40	6.41	7	32.96	9.15
45	23.65	5.93	18-21 h	35.71	6.50	8	37.18	9.25
90	41.28	6.54	22-24 h	35.75	6.63	9	41.11	9.37
120	68.87	10.69	1.25-2 d	34.03	7.01	10	44.82	9.46

^a Overall, RMSE = 28.36 cGy, RMSPE = 9.57%.

^b Root mean square error = $\sqrt{\text{ave}[(\text{EPD}-\text{approximation})^2]}$

^c Root mean square percentage error = $\sqrt{\text{ave}[(\text{EPD}-\text{approximation})^2/\text{EPD}^2]} \times 100\%$.

Figure 4. Comparison of model and approximation for two examples of Case 2.

Examples

1. Approximate EPD for $\Delta = 10$ min, $D' = 5$ cGy/min, and $t = 24$ h: Using Eq. (4), equivalent prompt dose is approximated as

$$\text{EPD} = 4.20 \times 5 \times 10^{0.775 - 0.0179 \times \log^2(24/48)} = 122.6 \text{ cGy} .$$

2. For $\Delta = 20$ min and $D' = 3$ cGy/min, approximate the time at which $\text{EPD} = 100$ cGy. First β is calculated as

$$\beta = 1.43 + 0.775 \times \log(20) + \log(3) = 4.850 .$$

This is greater than $\log(\text{EPD}) = \log(100) = 4.605$; so, using Eq. (4),

$$t = \min(48 \times e^{-7.47 \times \sqrt{(4.850 - 4.605)/\log(20)}}, 48) = \min(5.7 , 48) = 5.7 \text{ h} .$$

Had β been less than $\log(\text{EPD})$, the conclusion would have been that the specified equivalent prompt dose would not have been reached.

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