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Dose-Rate Dependence of High-Dose Health Effects in Humans from Photon Radiation with Application to Radiological Terrorism

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Executive Summary

In 1981, as part of a symposium entitled "The Control of Exposure of the Public to Ionizing Radiation in the Event of Accident or Attack," Lushbaugh, Hübner, and Fry published a paper examining "radiation tolerance" of various human health endpoints as a function of dose rate. This paper may not have received the notice it warrants. The health endpoints examined by Lushbaugh et al. were the lethal dose that will kill 50% of people within 60 days of exposure without medical care ($LD_{50/60}$); severe bone marrow damage in healthy men; severe bone marrow damage in leukemia patients; temporary sterility (azoospermia); reduced male fertility; and late effects such as cancer. Their analysis was grounded in extensive clinical experience and anchored to a few selected data points, and based on the 1968 dose-rate dependence theory of J.L. Bateman. The Lushbaugh et al. paper did not give predictive equations for the relationships, although they were implied in the text, and the relationships were presented in a non-intuitive way. This work derives the parameters needed in Bateman's equation for each health endpoint, tabulates the results, and plots them in a more conventional manner on logarithmic scales. The results give a quantitative indication of how the human organism can tolerate more radiation dose when it is delivered at lower dose rates. For example, the $LD_{50/60}$ increases from about 3 grays (300 rads) when given at very high dose rates to over 10 grays (1,000 rads) when given at much lower dose rates over periods of several months. The latter figure is borne out by the case of an individual who survived for at least 19 years after receiving doses in the range of 9 to 17 grays (900-1700 rads) over 106 days. The Lushbaugh et al. work shows the importance of sheltering when confronted with long-term exposure to radiological contamination such as would be expected from a radiological dispersion event, reactor accident, or ground-level nuclear explosion.

Contents

1.0 Introduction

With the current awareness of threats of radiological dispersion events (RDEs) or terrorist use of improvised nuclear devices (INDs), there is renewed interest in the dose-rate dependence of certain symptoms and health outcomes of high-dose radiation exposure, especially as might be experienced by populations exposed for prolonged periods to radiation from nuclear fallout or radioactive materials dispersed in the environment. Because of the well-known ability of organisms to repair radiation injury as long as it is not too serious, protracting exposures permits some repair to occur before additional dose is received. The result is that the amount of radiation absorbed dose, *D*, needed to produce a given set of symptoms increases for decreasing dose rate for photon radiation such as x- and γ-radiation (International Commission on Radiological Protection (ICRP) 1991; Lushbaugh, Hübner, and Fry 1982; Mettler and Upton 1995; National Council on Radiation Protection and Measurements (NCRP) 1974; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2001a; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2001b).

In 1981, as part of a symposium entitled “The Control of Exposure of the Public to Ionizing Radiation in the Event of Accident or Attack,” Lushbaugh, Hübner, and Fry (1982) published a paper examining “radiation tolerance” of various human health endpoints. The notion of a tolerance dose for radiation protection originated early in the 20th century, and was discussed in detail by Cantril and Parker (1945).

The Lushbaugh et al. (1982) analysis was grounded in extensive clinical experience and anchored to a few selected data points, and based on the dose-rate dependence theory of J.L. Bateman (1968). The Lushbaugh et al. paper did not give predictive equations for the relationships, although they were implied in the text, and the relationships were presented in a non-intuitive way. This brief work derives the parameters needed in Bateman’s equation, tabulates the results, and plots them in a more conventional manner on logarithmic scales. This report is intended to supplement an earlier work of Strom (2003).

2.0 Converting Photon Exposure in Roentgens to Absorbed Dose in Grays or Rads

The conversion between *exposure* , which is the ionization equivalent of collision kerma in air (Attix 1981), to *absorbed dose in tissue* depends on the photon energy spectrum (International Commission on Radiological Protection (ICRP) 1996) as well as the depth of the tissue in question. For bone marrow and an unspecified but fairly high energy spectrum, Lushbaugh et al. (1982) variously quote conversions from R to rads of “64 to 68 percent” (caption to Figure 4) and “rad = 0.66 Exposure R” (footnote to Table 3). One commentor from the UK, Dr. Spiers, states that the conversion should be 0.75 rad/R (quoted in “Discussion,” p. 59 following Lushbaugh et al. 1982 in the Proceedings).

This paper uses 1 Gy = 100 rads = 150 R as a conversion, that is, 1 R = 2/3 rad.

3.0 Bateman's Dose-Rate Equation

Bateman (1968) proposes a mathematical relationship for the dose-rate dependence of high-dose effects:

$$D_i(\dot{D}) = D_i(\infty)\left(1 + \frac{K_i}{\sqrt[3]{\dot{D}}}\right), \tag{1}$$

where the "isoeffective dose" D_i for the i^{th} effect at dose rate $\dot{D}_1$ is proportional to the dose producing the effect at infinite dose rate $D_i(\infty)$ multiplied by a term that increases above 1 as dose rate decreases from very high values. The second term in parentheses contains a slope parameter K_i for the i^{th} effect divided by the cube root of the dose rate. The units of K_i depend on the units of $\dot{D}$, so it is necessary to convert values of K_i found in Lushbaugh et al. (1982) to absorbed dose units of rads or grays. In Lushbaugh et al. (1982), K has dimensions of $(\text{R/min})^{1/3}$ as shown in the figure captions on pp. 54-55, since the expression in parentheses must be dimensionless. To convert to Gy/s, one must use the rad/R value of 2/3, one must convert minutes to seconds, and rads to grays.

4.0 Health Endpoints

Health endpoints considered by Lushbaugh, Hübner, and Fry (1982) include

- the lethal dose that will kill 50% of people in 60 days with no medical care (the $LD_{50/60}$)
- severe bone marrow damage in healthy men
- severe bone marrow damage in leukemia patients
- temporary sterility (temporary azoospermia)
- low male fertility
- and "late effects" (cancers and heritable ill-health).

Lushbaugh et al. (1982) also show the lower dose estimate for the one adult male who survived the 1962 Mexican ^{60}Co accident (Andrews 1963; Martinez et al. 1964) for at least 19 years[1].

The values used to derive parameters for Eq. (1) are discussed below for each endpoint in their original units. This is followed by the presentation of all relevant parameters in both traditional and modern SI units.

4.1 $LD_{50/60}$

The $LD_{50/60}$ value is discussed at length by Lushbaugh et al. It is is constrained to pass through a value of 450 R at 1.5 R/min and has a K of 0.65 $(\text{R/min})^{1/3}$ (caption to Lushbaugh et al. (1982) Figure 13).

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[1] Lushbaugh et al. (1982) was written and presented in 1981, and mistakenly identified the date of the accident as the year of publication of Martinez et al. (1964) rather than the date of the accident, which was 1962. The survivor was alive in 1981, making him a 19-year survivor (as opposed to 17 years quoted in Lushbaugh et al. 1982).

4.2 Severe Bone Marrow Damage

The lines for severe bone marrow damage are based on the model of Yuhas et al. (1972), and are constrained to pass through 100 R at 1.5 R/min for patients and 200 R at 1.5 R/min for normal men. The *K* for the patients is 0.237 and that for normal men is double, that is, 0.475.

4.3 Temporary Azoospermia and Low Male Fertility

The lines for temporary azoospermia and low male fertility are taken from the work presented in Langham (1967) on humans (high dose rate points) and of Cassarett and Eddy (1968) on dogs (low dose rate points). The line for low male fertility is constrained to pass through 110 R at 110 R/year, and 40 R at 1.5 R/min. The line for temporary sterility is constrained to pass through 220 R at 220 R/year, and 40 R at 1.5 R/min.

4.4 Late Effects

Late effects include cancer and heritable ill-health. The data are based on The work of the Radiobiological Advisory Panel of the National Research Council (National Research Council, Radiobiological Advisory Panel 1970). The line for late effects is constrained to pass through 80 R at 80 R/y and through 40 R at 40 R/min. This is tantamount to a dose and dose rate effectiveness factor (*DDREF*) of 2, that is, doses delivered at high dose rates are twice as effective as doses delivered at low dose rates.

4.5 Mexican Accident Survivor

The estimated doses to the Mexican accident survivor who was irradiated for 106 days at an estimated 4 to 6 mSv/hour (0.4 to 0.6 rem/hour) were 9.84 to 17.17 Sv (984-1717 rem). These dose equivalent numbers are taken to be equal to Gy and rad, respectively, for ^{60}Co radiation.

5.0 Results and Discussion

5.1 Table of Parameters and Graphs

The parameters $D(\infty)$ and K_i for Eq. (1) for these health effects are given in Table 1 in both traditional and SI units. The derivation of equations used to infer $D(\infty)$ and K_i is given in the Appendix.

Table 1. Values of the slope parameter K_i and dose at infinite dose rate $D(\infty)$ derived from Lushbaugh et al. (1982) for six health endpoints.

Endpoint *i*	K_i ([R/min]$^{1/3}$)	K_i ([Gy/s]$^{1/3}$)	$D(\infty)$ (R)	$D(\infty)$ (Gy)
$LD_{50/60}$	0.65	0.0312	449	2.99
Severe Marrow Damage (Normal Men)	0.475	0.0228	200	1.33
Severe Marrow Damage (Patients)	0.237	0.0114	99.9	0.666
Temporary Azoospermia	0.525	0.0253	39.9	0.266
Low Male Fertility	0.160	0.00767	40.0	0.267
Late Effects	0.0534	0.00257	40.0	0.267

"Tolerance doses" calculated using Eq. (1) and the parameters in Table 1 are given in Tables 2 (SI units) and 3 (traditional units) for selected dose rates.

Table 2. Calculated "tolerance doses" (in mGy) as a function of dose rate (in mGy/h) for six health endpoints using Eq. (1) and parameters in Table 1.

dose rate (mGy/h)	$LD_{50/60}$ (mGy)	Severe Marrow Damage (Normal Men) (mGy)	Severe Marrow Damage (Patients) (mGy)	Temporary Azoo-spermia (mGy)	Low Male Fertility (mGy)	10% Increase in Late Effects (mGy)
∞	2,995	1,330	666	266	267	267
10,000	3,660	1,550	720	314	281	272
1,000	4,430	1,800	783	369	298	277
100	6,080	2,340	917	488	334	289
10	9,650	3,490	1,210	745	412	315
1	17,300	5,990	1,830	1,300	580	372
0.1	33,900	11,400	3,170	2,490	942	493

Table 3. Calculated "tolerance doses" (in rads) as a function of dose rate (in rads/h) for six health endpoints using Eq. (1) and parameters in Table 1.

dose rate (rad/h)	$LD_{50/60}$ (rad)	Severe Marrow Damage (Normal Men) (rad)	Severe Marrow Damage (Patients) (rad)	Temporary Azoo-spermia (rad)	Low Male Fertility (rad)	10% Increase in Late Effects (rad)
∞	299	133	67	27	27	27
1,000	366	155	72	31	28	27
100	443	180	78	37	30	28
10	608	234	92	49	33	29
1	965	349	121	74	41	32
0.1	1,730	599	183	130	58	37
0.01	3,390	1,140	317	249	94	49

The original Figure 13 from Lushbaugh et al. (1982) is shown below as Figure 1. The constraints described above are shown as solid points on the various lines. Additionally, the lower estimate of the Mexican accident survivor dose is shown as an asterisk on the 3-month isochron. Lushbaugh et al. point out that there are no human data beyond 3 months, but that they have extrapolated the lines beyond one year.

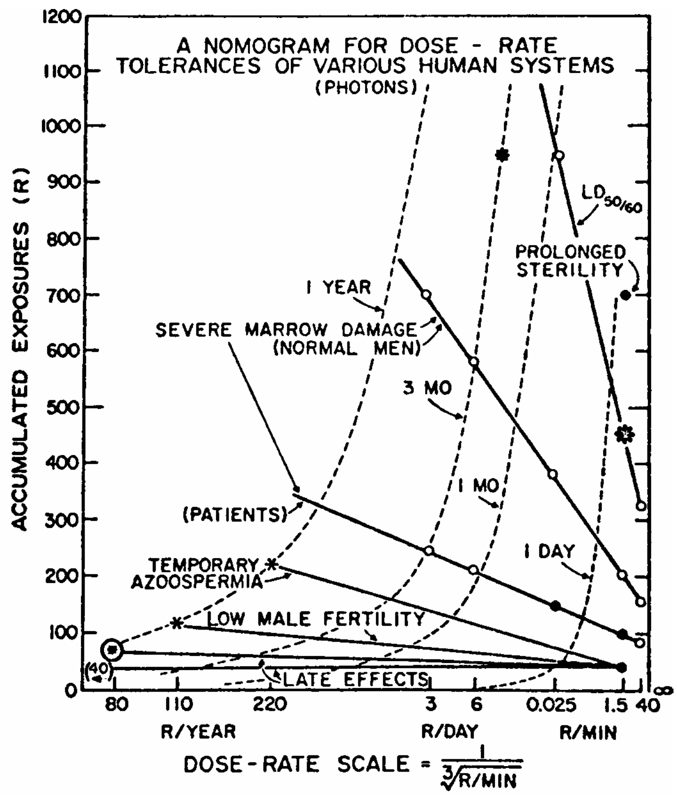

Fig. 1. "A nomogram for dose-rate tolerances of various human systems (photons)" from Lushbaugh, Hübner, and Fry (1982). Note that data and calculations are plotted on a dose-rate scale of $\dot{X}^{-1/3}$, where the zero point is labeled ∞, and the scale increases from right to left. There are at least two difficulties with this graph. First, the Mexican accident survivor data point that appears on the 3-month isochron is plotted at about 950 R, when the dose range quoted in the paper is 984-1717 *rems*. Using the conversion of 1 rad = 1 rem for photons, and 1 R = 2/3 rad, this range would be 1476-2576 R. The second difficulty is that the point labeled "Prolonged Sterility" is not discussed in the text, nor it is referenced. Finally, the plotted line for $LD_{50/60}$ doesn't appear to have the slope given in the text.

Predictions of Eq. (1) are replotted in Figure 2 on conventional logarithmic axes for the six health endpoints. Also shown in Figure 2 is the range of reconstructed doses in grays for the Mexican accident survivor.

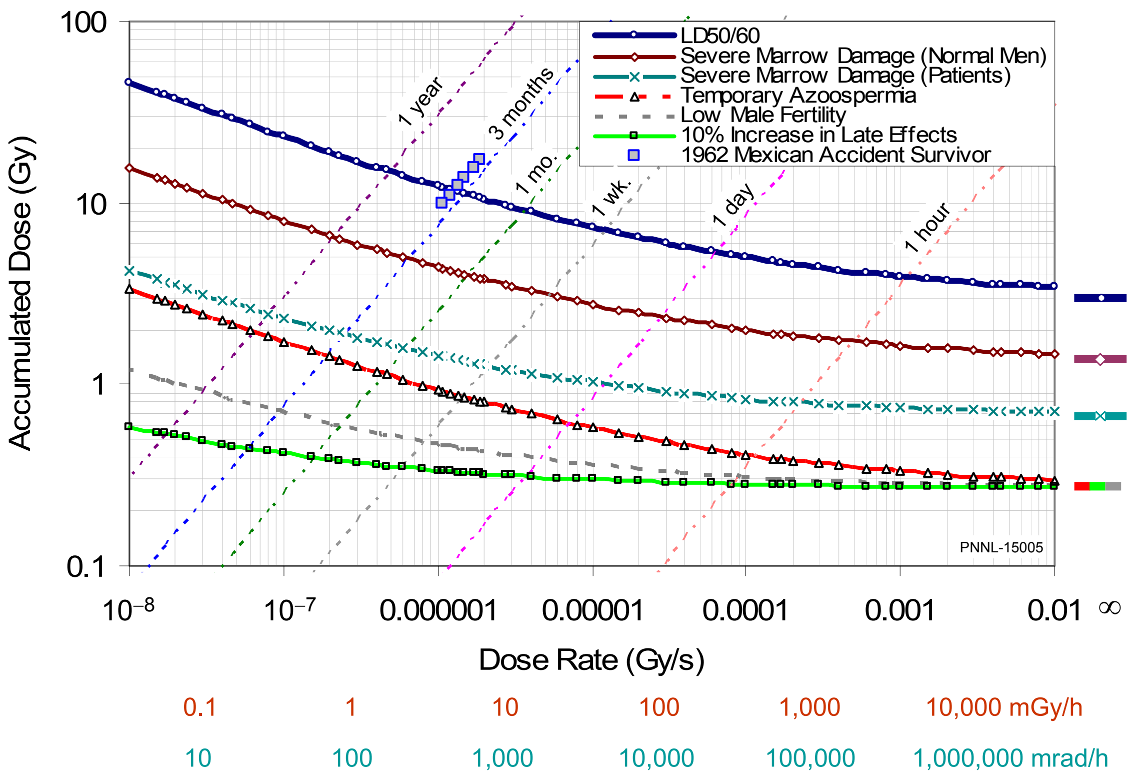

Fig. 2. Calculated "Tolerances of Various Human Systems" as a function of photon dose rate based on work by Lushbaugh, Hubner, and Fry (1982) using their conversion of 150 R ≈ 1 Gy. Straight diagonal lines are isochrons, that is, lines where $D / \dot{D} =$ a constant. From top to bottom, lines are $LD_{50/60}$, severe marrow damage to healthy men, severe marrow damage to leukemia patients, temporary sterility (azoospermia), reduced male fertility, and a 10% increase in late effects such as cancer and heritable ill-health. The series of larger squares show the range of dose estimates for the [at least] 19-year survivor of the 1962 Mexican accident, who was irradiated at "0.4-0.6 R/hr for 106 days." Bars on far right represent $D(\infty)$ for the various endpoints.

Figure 3 shows ranges of reconstructed doses for the five persons involved in the 1962 Mexican accident along with the $LD_{50/60}$ prediction from Lushbaugh et al. (1982). The daughter was 3 years old, the son was 10 years old, and the mother was 27 years old (Andrews 1963); ages for the father and grandmother were not given. The son was non-uniformly irradiated since he carried the 185-GBq (5 Ci) source in his pocket for some two weeks, while the others were more or less uniformly irradiated while the source was stored in a kitchen cabinet (Andrews 1963).

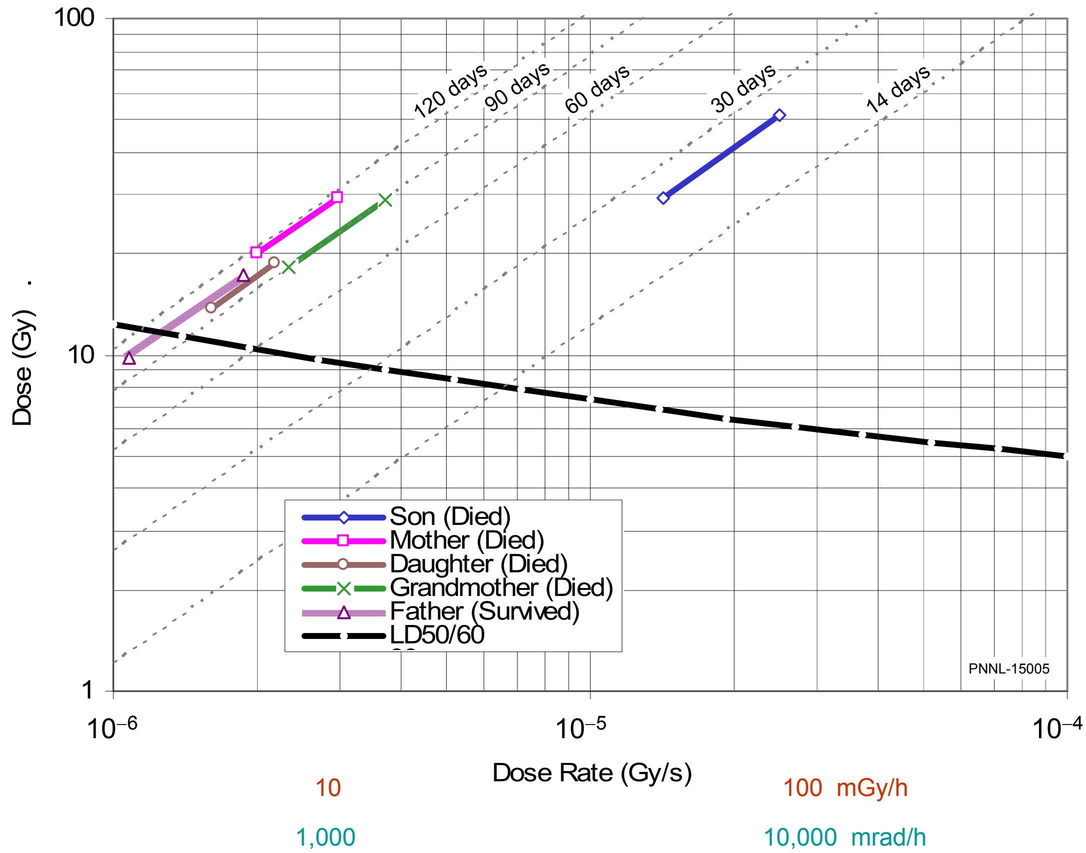

Fig. 3. Dose ranges for the five persons involved in the 1962 accident in Mexico with isochrons from 14 days to 120 days.

5.2 Discussion

Figure 2 and Tables 2 and 3 clearly show the increase in calculated "tolerance dose" for six human health endpoints as photon dose rate decreases. While there are no human data cited for irradiation periods beyond 106 days, the range of doses for the survivor of the 1962 accident in Mexico are consistent with the increase in the $LD_{50/60}$ from about 3 Gy at very high dose rates to over 10 Gy at lower dose rates.

This work extends the simple "Penalty Table" of Report No. 42 (NCRP 1974) to six health endpoints at any dose rate.

The fact that the Mexican accident survivor was out of the house where the source was stored for 8 or more hours per day means that his bone marrow had repeated opportunities for small recovery before being subjected to irradiation again. The implications for survivability in a contamination zone are clear: periodic sheltering can enhance repair and improve chances of survival.

Amazingly enough, the predictions of late effects made in 1970 imply a dose and dose-rate effectiveness factor (*DDREF*) of 2 (80 R [~ 0.533 Gy] at low dose rate causes the same level of effect as 40 R [~ 0.266 Gy] at high dose rate), the same as used by the ICRP (1991), and the predictions are virtually identical. Lushbaugh et al. state that “the encircled asterisk is the conjectured (NASA Space Radiation Study Panel) dose of 80 R/yr that might cause a 10 percent increase in late effects such as cancer.” Assuming roughly 40% fatal cancer, non-fatal cancer, and heritable ill-health, a 10% increase would be a 4% absolute increase. The 4.0% absolute increase per 0.533 Gy translates to 7.5% per gray. The ICRP (1991, Table 2) uses a figure of 7.3% total detriment per sievert, which is the same as 7.3% per gray for photon radiation. The agreement between the 1970 NASA estimated risk factor and the more recent ICRP risk factor is essentially exact.

6.0 Conclusions and Recommendations

This review of the work by Lushbaugh et al. published in 1982 gives insights into predicting the dose-rate dependence of six high-dose human health endpoints. Since prolonged exposure to photon radiation at lower dose rates is a likely consequence of radiological dispersion events or nuclear explosions, it is important to understand responses to relatively high doses delivered at low dose rates.

Future work should include theoretical determination of “tolerance doses” in time-varying dose rates such as would be experienced with radioactive decay of fallout or deliberate or accidental dispersion of shorter lived sources such as ^{192}Ir, or with weathering and decontamination of long-lived contamination. Additionally, future work should include distributions of “tolerance doses” to show variability across a population of differing age, sex, and radiation sensitivity.

7.0 References

1. Andrews GA. 1963. "Mexican Co-60 Radiation Accident." Isotopes and Radiation Technology 2(1):200-201.

2. Attix FH. 1981. "Radiation Quantities and Units. ICRU Report 33." Health Physics 41(1):210-213.

3. Bateman JL. Relation of Irradiation Dose-Rate Effects in Mammals and in Mammalian Cells. 23.1-23.19. 1968. Springfield, Virginia, National Technical Information Service. Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology. USAEC Report CONF-680410.

4. Cantril ST and HM Parker. 1945. *The Tolerance Dose*. MDDC-1100; CH-2812, U.S. Atomic Energy Commission, Oak Ridge, Tennessee.

5. Casarett GW and HA Eddy. Fractionation of Dose in Radiation-Induced Male Sterility. 14.1-14.10. 1968. Springfield, Virginia, National Technical Information Service. Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology. USAEC Report CONF-680410.

6. International Commission on Radiological Protection (ICRP). 1996. "Conversion Coefficients for Use in Radiological Protection Against External Radiation. ICRP Publication No. 74." Annals of the ICRP 26(3-4).

7. International Commission on Radiological Protection (ICRP). 1991. "1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication No. 60." Annals of the ICRP 21(1-3).

8. Langham WH. 1967. *Radiobiological Factors in Manned Space Flight*. NRC Publication 1487, National Academy of Sciences, Washington, DC.

9. Lushbaugh CC, KF Hübner, and SA Fry. 1982. "The Impact of Estimates of Human Radiation Tolerance upon Radiation Emergency Management." Chapter 4A in *The Control of Exposure of the Public to Ionizing Radiation in the Event of Accident or Attack. Proceedings of a Symposium Sponsored by the National Council on Radiation Protection and Measurements, April 27-29, 1981, Reston, Virginia*, eds. LV Spencer, LS Taylor, JC Greene, DW Bensen, and R Park, pp. 46-57. National Council on Radiation Protection and Measurements, Bethesda, Maryland.

10. Martinez GR, HG Cassab, GG Ganem, KE Guttman, LM Lieberman, BL Vater, MM Linares, and MH Rodriquez. 1964. "Observaciones Sobre la Exposicion Accidental de Una Famila a Una Fuente de Cobalto 60." Rev.Med.Inst.Mex.Seguro Social 3(Suppl. 1):14-68.

11. Mettler FA and AC Upton. 1995. *Medical Effects of Ionizing Radiation*. Saunders, Philadelphia.

12. National Council on Radiation Protection and Measurements (NCRP). 1974. *Radiological Factors Affection Decision-Making in a Nuclear Attack*. Report No. 42, Superintendent of Documents, Washington, D.C.

13. National Research Council, Radiobiological Advisory Panel. 1970. *Radiation Protection Guides and Constraints for Space Mission and Vehicle-Design Studies Involving Nuclear Systems*. National Academy of Sciences, Washington, DC.

14. Strom DJ. 2003. *Health Impacts from Acute Radiation Exposure*. PNNL-14424, Pacific Northwest National Laboratory, Richland, Washington.

15. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). 2001a. *Sources and Effects of Ionizing Radiation: UNSCEAR 2000 Report to the General Assembly, with Scientific Annexes. Vol. I: Sources*. United Nations, New York.

16. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). 2001b. *Sources and Effects of Ionizing Radiation: UNSCEAR 2000 Report to the General Assembly, with Scientific Annexes. Vol. II: Effects*. United Nations, New York.

17. Yuhas JM, TR Stokes, and CC Lushbaugh. 1972. "Multifactorial Analysis of Human Blood Cell Responses to Clinical Toatal-Body Irradiation." in *Proceedings of the National Symposium on Natural and Manmade Radiation in Space, Las Vegas. NASA TM X-2440*,

ed. EA Warman, pp. 233-237. National Technical Information Service, Springfield, Virginia.

Appendix: Derivation of Parameters for Bateman's Equation from Data Given in Lushbaugh, Hübner, and Fry (1982)

For $LD_{50/60}$, severe marrow damage in normal men, and severe marrow damage in leukemia patients, Lushbaugh et al. (1982) presented values of K_i. Given a dose, dose rate pair $\left(D_i(\dot{D}_1), \dot{D}_1\right)$, one can solve Eq. (1) for $D_i(\infty)$ in terms of K_i and the dose, dose rate pair:

$$D_i(\infty) = \frac{D_i(\dot{D}_1)}{1 + \frac{K_i}{\sqrt[3]{\dot{D}_1}}}. \tag{2}$$

The values given in Sections 4.1 and 4.2 were substituted into Eq. (2) to yield the $D_i(\infty)$ values in Table 1.

For temporary azoospermia, low male fertility, and late effects, one is given two dose, dose rate pairs. Then one must first solve Eq. (1) for K_i, substituting $\left(D_i(\dot{D}_2), \dot{D}_2\right)$:

$$K_i = \sqrt[3]{\dot{D}_2}\left(\frac{D_i(\dot{D}_2)}{D_i(\infty)} - 1\right) \tag{3}$$

Eliminating $D_i(\infty)$ from Eq. (3) by substituting Eq. (2) into Eq. (3) and solving for K_i, one has

$$K_i = \frac{\sqrt[3]{\dot{D}_2}\left(\frac{D_i(\dot{D}_2)}{D_i(\dot{D}_1)} - 1\right)}{1 - \sqrt[3]{\frac{\dot{D}_2}{\dot{D}_1}}\frac{D_i(\dot{D}_2)}{D_i(\dot{D}_1)}}. \tag{4}$$

The values given in Sections 4.3 and 4.4 were substituted into Eq. (4), and the resultant value of K_i was substituted into Eq. (2) to yield the K_i and $D_i(\infty)$ values in Table 1.