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Models for Pulmonary Lethality and Morbidity After Irradiation From Internal and External Sources

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Commission

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OTHER DOCUMENTS IN SERIES

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Filipy, R. E., Decker, J. R., Lai, Y.-L., Lauhala, K. E., Buschbom, R. L., Hlastala, H. P., McGee, D. R., Park, J. L., Kuffel, E. G., Ragan, H. A., Cannon, W. C., Yaniv, S. S., and Scott, B. R. (1988): Inhaled $^{239}PuO_2$ and/or Total-Body Gamma Radiation: Early Mortality and Morbidity in Rats and Dogs. U. S. NRC Report NUREG/CR-5198. Available for purchase from National Technical Information Service, Springfield, VA 22161.

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ABSTRACT

This report provides a hazard-function model for estimating the risk of death from radiation pneumonitis and/or pulmonary fibrosis following a light-water nuclear power plant accident. A similar model is also provided for estimating the prevalence of respiratory functional morbidity among those that survive death from acute effects. Hazard-function models for lethality and for morbidity were constructed using the cumulative hazard estimator H, which is related to the risk estimator R through the equation $R = 1-\exp(-H)$. The estimator H can be calculated using information provided in the report. The method of calculation depends on the exposure scenario. In general, the total normalized dose X for lethality or for morbidity is calculated. For lethality, $X = 1$ corresponds to a median lethal dose (LD_{50}); for morbidity, $X = 1$ corresponds to a median effective dose (ED_{50}). H is related to X by the equation $H = \ln(2)X^{V}$, where V depends on the type of radiation (or radiations) involved. Contributions to X can arise from each of two main modes of exposure: (1) Brief exposure of the lung, at a relatively high dose rate, to mainly external gammas, followed by (2) chronic internal alpha, and/or beta, and/or gamma irradiation of the lung. Equations are provided for calculating the contributions to X from both modes of exposure.

While uncertainty evaluation is important for any risk assessment, an evaluation of the uncertainties related to predicting lethality and morbidity cases after a nuclear accident is beyond the scope of this report. However, uncertainties are discussed in detail in a separate, follow-on report (NUREG/CR-4214) to be published in 1989.

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ACKNOWLEDGEMENTS

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EXECUTIVE SUMMARY

Dose-response (hazard-function) models for early and continuing health effects of exposure of the lung to mixed radiations (alpha, beta, and gamma) have been developed for use in probabilistic analyses of light-water nuclear power plant accident consequences. The recent nuclear power plant accident at Chernobyl demonstrated that such an accident can lead to brief external exposure to gamma radiation along with chronic internal exposure due to complex mixtures of inhaled radionuclides. Animal studies have demonstrated that chronic irradiation of the lung by internally deposited radionuclides can lead to death from radiation pneumonitis and/or pulmonary fibrosis (RPPF).

This report provides a hazard-function model for estimating the risk of death from RPPF following a light water nuclear power plant accident. A similar model is also provided for respiratory functional morbidity caused by irradiation of the lung. Respiratory functional morbidity is defined as abnormalities in any three or more of the following respiratory functions: vital capacity, [illegible]static compliance, CO diffusing capacity, and ventilation distribution.

Dose-response models were constructed based on use of the cumulative hazard which is estimated by the estimator H. The risk estimator R was constructed as a function of the cumulative hazard estimator H using the equation

$$R = 1 - \exp(-H).$$

The estimator H depends on the normalized dose X, where the normalized dose (a theoretical dose) represents a dose in units of D_{50} (i.e., LD_{50} or ED_{50}). A normalized lethality dose of X = 1 corresponds to the median lethal dose, LD_{50}; a normalized morbidity dose of X = 1 corresponds to a median effective dose, ED_{50}. Using a form of the Weibull model, which has been demonstrated to be quite useful for modeling dose rate and mixed-radiation effects, H is related to X by the equation

$$H = \ln(2)X^{V},$$

where the shape parameter V is positive. The shape parameter determines the shape of the dose-effect curves for lethality and for morbidity. For lethality from RPPF and for respiratory functional morbidity, V is estimated to be about 12 for brief external gamma irradiation, and about 5 for chronic internal alpha and/or beta irradiation of the lung.

Unlike absorbed doses from alpha- and beta-emitting radionuclides, normalized alpha and beta doses can be added when the shape parameter is the same for both radiations. Normalized alpha and beta doses are therefore added to obtain their contribution to the total normalized dose. To calculate the normalized dose for death from RPPF after brief external gamma irradiation of the lung, the cumulative absorbed dose is divided by the D_{50}, which is estimated to be 1000 rad (10 Gy). Because the shape parameter for external gamma irradiation differs from that for internal alpha and/or beta irradiation, the external gamma normalized dose must be raised to the 2.4 power to obtain an "isoeffect" dose that can then be added to the normalized alpha dose and/or beta dose to obtain the total normalized dose. The exponent 2.4 is the ratio of the shape parameters for external gamma irradiation (V = 12) to that for internal alpha and/or beta irradiation (V = 5). The exponent of 2.4 is specific for scenarios where the external gamma-ray exposure is brief and is followed by chronic, exponentially decaying patterns of alpha and/or beta irradiation of the lung due to inhaled radionuclides. Also, the exponent 2.4 applies only to death from RPPF and to respiratory functional morbidity.

To calculate the normalized dose for death from RPPF after chronic alpha irradiation of the lung, the cumulative absorbed alpha dose to the lung is divided by the D_{50} for chronic alpha irradiation, which is estimated to be 3500 rad (35 Gy), based on an analysis of 3-year follow-up data for dogs exposed by inhalation to $^{239}PuO_2$. With longer follow-up, a smaller D_{50} might be found. Also, for brief exposure to alpha particles at a high dose rate, the D_{50} is likely to be much smaller than 3500 rad. We expect that it would be less than the 1000 rad (10 Gy) value found for brief exposure to external gamma rays.

To calculate the normalized dose for death from RPPF after chronic beta irradiation of the lung, the absorbed beta radiation dose that occurs in three consecutive time intervals can be divided by fixed normalization parameters appropriate for the interval to obtain the normalized doses associated with the intervals (fixed-parameter model). The absorbed doses and normalization parameters are expressed in the same units. The absorbed beta dose that accumulates between 0 and 14 days, which is presumed to be due mainly to short- and intermediate-lived radionuclides, is divided by a fixed normalization parameter of 16000 rad (160 Gy) to obtain the dose X for that time interval. The absorbed beta dose that accumulates within the 14-200 day interval, which is presumed to be due mainly to intermediate- and/or long-lived radionuclides, is divided by the fixed normalization parameter of 37000 rad (370 Gy) to obtain the normalized dose for the 14-200 day interval. The absorbed beta dose that accumulates within the 200-365 day interval, which is presumed to be mainly due to long-lived radionuclides, is divided by the fixed normalization parameter 92000 rad (920 Gy) to obtain the normalized dose for the remainder of the exposure. The normalization parameters used in the fixed-parameters model were derived from data for chronic beta irradiation of the lung of dogs, with deaths from RPPF occurring after 365 days also included when estimating model parameters.

Respiratory functional morbidity normalized doses are calculated in a similar way with D_{50}'s and normalization parameters used for lethality from RPPF reduced by a factor of 2 for morbidity.

The fixed-parameter, lethality and morbidity models presented are specific for light-water reactor accident health risk assessment. For other nuclear disasters, different types of exposure patterns could arise. To calculate the normalized beta and/or gamma dose for any continuous pattern of irradiation of the lung, an empirical dose-rate model was developed for predicting the D_{50} for lethality or morbidity as a function of the average absorbed dose rate to the lung for a small interval of exposure time. Dividing the absorbed beta and/or gamma dose by the dose-rate-dependent D_{50} provides an estimate of the normalized dose for the small interval. Evaluating normalized beta and/or gamma doses for consecutive small time intervals and adding them provides a means of estimating the total normalized dose for any continuous pattern of beta and/or gamma irradiation of the lung.

For simultaneous alpha, beta, and gamma irradiation of the lung, the shape parameter for lethality or morbidity depends on the fraction of the total normalized dose due to alphas (g_a), betas (g_b), and gammas (g_a). To estimate V, the following empirical model is proposed:

$$1/V = 1/V_{abg} = g_a/5 + g_b/5 + g_g/12,$$

where V_{abg} is the predicted shape parameter for the simultaneous exposure. The plausibility of the above model for predicting the shape parameter for simultaneous exposure is discussed in Appendix B.

For some exposure patterns, analytical solutions for the normalized dose X can be found. An analytical solution is provided in Appendix A for the special case where the beta and/or gamma dose rate to the lung decreases as a negative exponential function of time. With the dose-rate model, the D_{50}'s for gamma and for beta irradiation of the lung are assumed to be the same.

While uncertainty evaluation is important for any risk assessment, an evaluation of the uncertainties related to predicting lethality and morbidity cases after a nuclear accident is beyond the scope of this report. However, uncertainties will be discussed in detail in a separate, follow-on report to a 1985 report (NUREG/CR-4214 SAND85-7185). The follow-on report is scheduled to be published in 1989.

CHAPTER 1
INTRODUCTION

For more than a decade, a major concern of the Nuclear Regulatory Commission (NRC) and the general public has been the health effects of potential accidental releases of radionuclides from nuclear power plants. Computer simulation models have been developed to evaluate the aggregate risk of potential nuclear accidents at many reactors and sites (Alpert et al., 1986). In 1975, the NRC issued the Reactor Safety Study (WASH 1400, 1975), which provided health effects models (HEM) for quantitative estimation of the health impacts of such accidents. The HEM provided the basis for most of the official estimates made in recent years of the potential health consequences of nuclear power plant accidents. In 1985 the HEM were revised (Evans et al., 1985). Additional revisions were also made after 1985. The models were used in the computer code MACCS developed by Sandia National Laboratory for the NRC (Alpert et al., 1986).

This report summarizes the most recently revised fixed-parameter models developed for use by the NRC (Scott and Hahn, 1985), for lethality and morbidity from irradiation of the lung, including modifications made since 1985 due to recent experimental and theoretical results (Filipy et al., 1988, 1989; Scott et al., 1987, 1988a, 1988b). A major modification is the inclusion of a term in the dose-response models for effects of chronic alpha irradiation. When the lethality model is coupled with other models for acute lethality from competing modes of death (marrow or gastrointestinal), a competing modes of death model can be obtained for nuclear accident risk assessment (Scott and Hahn, 1985, 1989).

Results of experiments carried out that relate to development of the refined models for morbidity and lethality are described in other publications (Scott et al., 1987, 1988b; Filipy et al., 1988, 1989). The primary form of morbidity addressed in the experiments was pulmonary function impairment. Body mass was found to be an indicator of morbidity only for those with impending death, and pertubations of circulating blood cell concentrations were of little clinical consequence with nonlethal doses. Related early theoretical developments are also discussed in other documents (Hahn, 1979; Filipy et al., 1980).

CHAPTER 2
EARLY AND CONTINUING EFFECTS IN MAN

2.1 NATURE OF EFFECTS

Early radiation effects could be induced in the lung with sufficient absorbed radiation doses following a nuclear accident. Pulmonary irradiation may be the result of total- or partial-body exposure to external photons or from radionuclides inhaled and deposited in the lung. Death from pulmonary injury could occur if a lethal lung burden of radionuclides is inhaled. More likely, however, is death following a combination of a nonlethal external dose to the total body and radionuclides deposited in the lung.

2.2 CHERNOBYL ACCIDENT VICTIMS

Following the nuclear power plant accident at Chernobyl in the Soviet Union (USSR, 1986; NUREG 1250, 1987; U. S. Department of Energy, 1987; U. K. Atomic Energy Authority, 1987; NEA, 1988; Mould, 1988), the most severe early-occurring radiation-related effect was death following combined injury to the bone marrow, intestine, lung, and skin (burns). Both external photons and inhaled radionuclides contributed significant radiation doses to firefighters and others that received radiation exposures in the median lethal or higher ranges (Gus'kova, 1987).

The exposure rate (in Sv/hr) due to the Chernobyl accident decreased with distance from the accident according to the approximation

$$\text{Exposure Rate} = 6.9*(\text{distance in kilometers})^{-1.4}$$

(Hohenemser and Renn, 1988). There were no distinct breaks between local dispersion and the distant radionuclide deposits when rainfall effects were accounted for; in general, the farther a country was from Chernobyl, the lower its average deposition (Hohenemser and Renn, 1988). This means that for similar nuclear accidents, the external exposure rate can be expected to decrease with distance from the accident in proportion to distance to the negative 1.4 or a similar power. Because the risk of death from acute effects of external photon irradiation of the lung increases initially in proportion to dose to about the 12th power, for doses above a threshold dose of about 500 rad (5 Gy) (Scott and Hahn, 1989), the risk of inducing death from acute effects in lung will decrease very rapidly with distance from a nuclear accident. However, at a given distance from the Chernobyl accident, rainfall locations exhibited activities 15 to 20 times higher than dry locations and thus rainfall can lead to an elevation in risk (Hohenemser and Renn, 1988).

Acute radiation pneumonitis was observed in seven victims heavily irradiated at the Chernobyl accident site (Gus'kova, 1987). Ventilatory failure occurred within 3 days, followed by death from hypoxemic coma. At autopsy, large blue lungs were found, with marked interstitial edema, and with no signs of destruction of the mucosa of the trachea or bronchi. Generally, interstitial pneumonitis developed a few days before death in combination with extremely severe skin burns and intestinal lesions. Deaths (not necessarily due only to injury to the lung) occurred 14-30 days after irradiation. Secondary viral infection was also a complicating factor.

The distributions of the relative activity of specific radionuclides (^{134}Cs, ^{131}I, ^{95}Zr, ^{140}La, ^{144}Ce, ^{141}Ce) taken from specific sites (Fig. 2.1) in the lungs of a Chernobyl victim are shown in Figure 2.2 (from USSR, 1986). The results indicate that the higher concentrations were at the periphery of the lung. The radionuclides given in Figure 2.2 probably contributed significantly to lung injuries following the Chernobyl accident. Large depositions of inhaled radionuclides could produce morbidity associated with respiratory dysfunction (respiratory functional morbidity) and lethality from radiation pneumonitis and/or pulmonary fibrosis (RPPF) as

has been demonstrated with laboratory animals (Filipy et al., 1988, 1989; Scott et al., 1987; Mauderly et al., 1973, 1980a, 1980b).

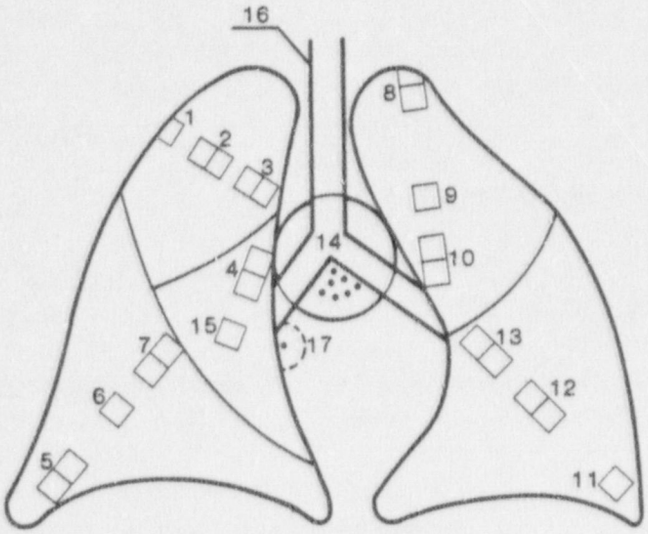

Figure 2.1 Scheme for selection of samples of dissected lung material from a victim of the Chernobyl nuclear acident (USSR, 1986). See Figure 2.2 for distribution of activity of specific radionuclides among these sections.

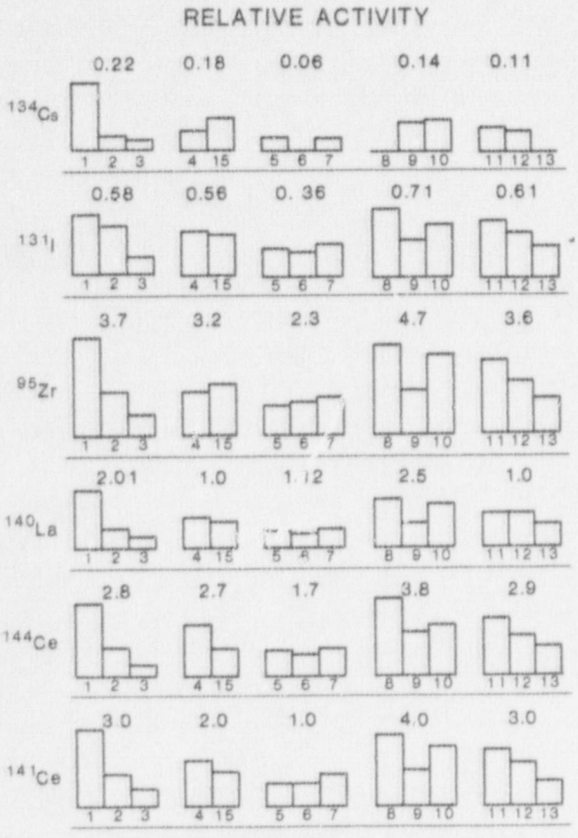

Figure 2.2 Distribution of specific radionuclides over the lungs of a victim of the Chernobyl nuclear accident (see Fig. 2.1 for scheme for selection of lung samples) (USSR, 1986). Size of vertical displacement based on approximate relative (average) value.

2.3 RADIATION THERAPY PATIENTS

The lung is a major dose-limiting organ in the delivery of sufficiently high single or fractionated doses of radiation to eradicate malignant diseases involving the thorax (Ellis, 1968). The diseases include primary lung tumors, Hodgkin's disease, esophageal cancer, breast cancer, and occult metastases from distant primary tumors (Travis, 1987b). Despite the absence of symptomatic changes, almost all patients receiving radiotherapy involving even a small portion of the thorax will receive some degree of pulmonary damage.

Rubin and Casarett (1968) reviewed the earlier reports of pulmonary damage which began with the use of higher energy therapy machines in the 1920's. More recently, Gross (1977) and Bortin (1983) have provided reviews. The reviews point out that radiation is frequently used in combination with other cytotoxic or immunosuppressive drugs or chemicals.

Some subgroups of the population may be more sensitive to the development of radiation pneumonitis than others. Factors that have been suggested to contribute to sensitivity are atherosclerosis, age, and underlying infection (Gross, 1977). Underlying infection was a complicating factor among victims of the Chernobyl nuclear accident (Gus'kova, 1987).

Early data, based on radiation therapy without cytotoxic or immunosuppressive drugs, tended to discount the importance of age (McKintosh and Spitz, 1939). Rubin and Casarett (1968) suggested that age may not be as important a factor in radiation sensitivity of the lung as it is for other tissues. Recent information on the importance of age at exposure comes from patients treated with total-body irradiation and bone marrow transplantation. Many were also treated with cytotoxic and immunosuppressive drugs. In one analysis (Weiner *et al.*, 1986), a two-fold increase in the incidence of interstitial pneumonitis was observed in patients over 21 years of age, as compared to younger ages. The finding was consistent with results of an earlier publication that demonstrated an increase in the relative risk for interstitial pneumonia with increasing age (Meyers *et al.*, 1982).

CHAPTER 3
EARLY AND CONTINUING EFFECTS IN ANIMALS

3.1 NATURE OF EFFECTS

Studies in experimental animals have focused both on the early and continuing effects of brief thoracic photon irradiation and of protracted internal alpha or beta irradiation of the lungs of mammals. Although the histologic descriptions of radiation pneumonitis have been based primarily on observations in laboratory animals after external thoracic irradiation, similar changes have also been observed with inhaled radionuclides (Slauson et al., 1976, 1977).

3.2 BRIEF THORACIC EXPOSURE

Studies involving laboratory animals have helped to clarify the shape of the dose-response relationship for death from RPPF after brief thoracic irradiation (Cardozo et al., 1985; Hill, 1983; Travis and De Luca, 1985; Miller et al., 1986; Collis and Steel, 1982; Kurohara and Casarett, 1972; Seimann et al., 1982; Ward et al., 1982; Dunjic et al., 1960; Phillips and Margolis, 1972; Travis and Down, 1981). Results are shown in Figure 3.1 in which the incidence of deaths from RPPF is plotted as a function of the normalized dose X (a theoretical dose that functions in a similar way as rem and Sv doses), where X is obtained by dividing the absorbed radiation dose D by the LD_{50} (Scott and Hahn, 1989; Scott et al., 1987, 1988a).

The dose X is dimensionless and X = 1 corresponds to a median lethal dose; X = 0.5 corresponds to 1/2 of the median lethal dose. The data in Figure 3.1 were fitted with the two-parameter Weibull model (smooth curve) discussed in Chapter 4. Use of the normalized dose X allows one to plot on the same curve, data originally expressed in ret, rem, rad, and etc., or data obtained at different dose rates or different photon energies (e.g., low-energy X rays, high-energy X rays, and gamma rays) (Scott and Hahn, 1989; Scott et al., 1988a; Filipy et al., 1988, 1989).

Note that the dose-response curve in Figure 3.1 is quite steep, suggesting a threshold at about 50% (i.e., X = 0.5) of the median lethal dose. In Figure 3.2, we have shown that the smooth curve in Figure 3.1 obtained from animal data adequately predicts the dose-response data for the incidence of radiation pneumonitis in man, when the normalized dose X is used (Scott and Hahn, 1989).

Since radiation pneumonitis in man is lethal in most clinically diagnosed cases (Fryer et al., 1978), the dose-response curve in Figure 3.2 for the incidence of radiation pneumonitis was used as an estimator for predicting the incidence of death from RPPF in man after brief exposure of the lung to external photons (Scott and Hahn, 1989). For brief exposures at very high dose rates that overwhelm recovery and repair, the dose in rad to the lung that corresponds to the normalized dose X is obtained by multiplying X by the median lethal dose at 1000 rad (10 Gy) (Scott and Hahn, 1989).

3.3 PROTRACTED EXPOSURE

3.3.1 External Irradiation

Protracted thoracic exposure to external photon radiation at low average dose rates (Hill, 1983) or repeated exposures at high instantaneous dose rates (Travis et al., 1987; Travis, 1987a, 1987b; Giri et al., 1985) is less injurious to the lungs of mice and rats than a brief single exposure. The sparing effect of protracted or fractionated exposure is mainly due to two homeostatic mechanisms: (1) intracellular repair and (2) repopulation of cells. Intracellular repair occurs mainly between repeated exposures and is complete within about four hours following a single, brief exposure. Repopulation of cells may occur at variable rates governed by

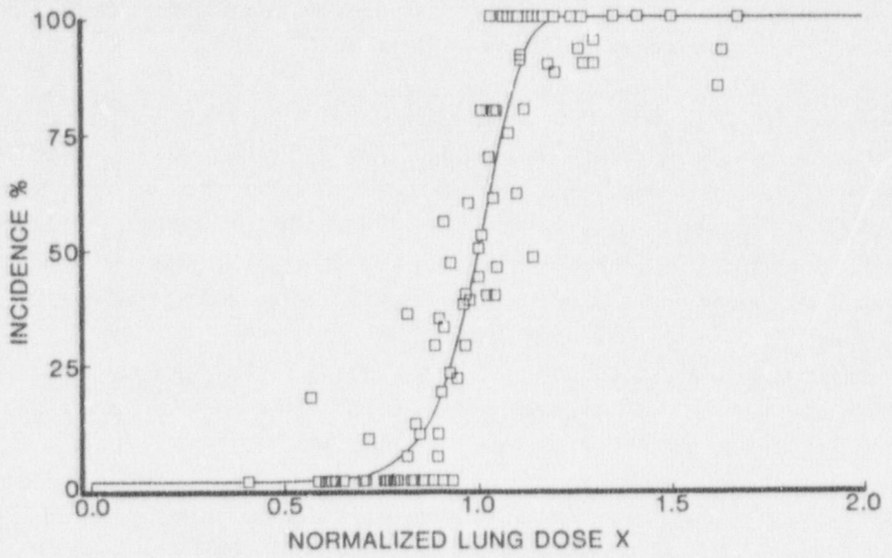

Figure 3.1 Dose-response relationship for incidence of acute lethality (160-210 day) from pulmonary injury after single, thoracic (photon) irradiation of mice and rats (Cardozo et al., 1985; Hill, 1983; Travis and De Luca, 1985; Miller et al., 1986; Collis and Steel, 1982; Kurohara and Casarett, 1972; Siemann et al., 1982; Ward et al., 1982; Dunjic et al., 1960; Phillips and Margolis, 1972; Travis and Down, 1981). Use of the normalized dose X in units of D_{50} eliminated much of the variability associated with units of dose, strain, species, and dose rate. Figure taken from previous publication (Scott and Hahn, 1989). The shape parameter in the Weibull model (see Section 4.3) was 12.

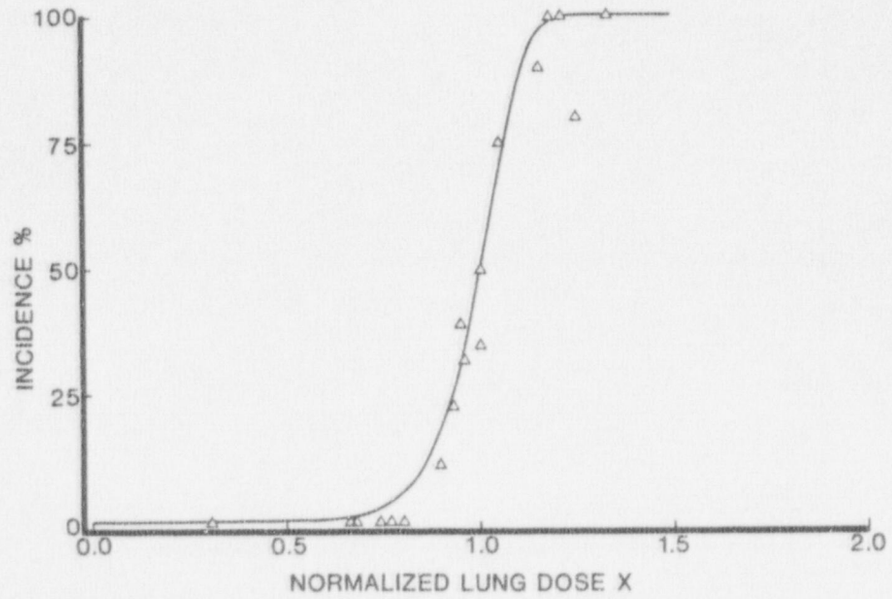

Figure 3.2 Dose-response relationship for incidence of radiation pneumonitis in man after single, thoracic photon irradiation or after fractionated irradiation with calculation of the equivalent dose administered in a single exposure. Results are expressed as a function of the normalized dose X in dimensionless units of the median lethal dose. Use of the normalized dose eliminates variability in the dose-response data due to different dose units (e.g., ret, rad, ED, etc.). The smooth curve is the same as in Figure 3.1 and is based solely on animal data. For high dose rate exposure, X = 1 corresponds to about 1000 rad (10 Gy) to the lung (Scott and Hahn, 1988). The data are from Van Dyk et al., 1981; Prato et al., 1977; Mah et al., 1987; and Phillips and Margolis, 1972).

homeostatic mechanisms (Thames and Hendry, 1987). For protracted exposure, repopulation of cells as well as intracellular repair may occur during irradiation.

3.3.2 Internal Irradiation

3.3.2.1 Lethality and Morbidity After Beta Irradiation

Inhaled high-energy beta-emitting radionuclides (^{90}Y, ^{91}Y, ^{90}Sr + ^{90}Y equilibrium mixtures, or ^{144}Ce) have been shown to induce death from RPPF in dogs that inhaled the radionuclide in insoluble fused aluminosilicate particles (McClellan et al., 1982). The use of insoluble fused aluminosilicate particles assured that irradiation would occur mainly in the lung. While beta energies for the four experiments were similar, the effective half-lives in the lung were different, resulting in different patterns of irradiation.

The different retention and dose-accumulation patterns are shown in Figures 3.3 and 3.4 for the four experiments. Average exposure time was the shortest for the ^{90}Y study and progressively increased for the ^{91}Y, ^{144}Ce, and ^{90}Sr experiments, respectively.

Different patterns of irradiation led to different dose-response relationships for lethality from RPPF, with the effectiveness decreasing as the average exposure time increased. Results for the ^{90}Y, ^{91}Y, and ^{144}Ce experiments are shown in Figure 3.5 along with dose-response relationships obtained for brief upper-body photon irradiation of rats based on data from Dunjic et al. (1960) and for the induction of radiation pneumonitis in man after brief thoracic photon irradiation (Van Dyk et al., 1981). The dose-response relationship for ^{90}Sr (not shown) was similar to that obtained for ^{144}Ce (Scott and Seiler, 1984). The rats used by Dunjic et al. were somewhat more sensitive than other rodents (Cardozo et al., 1985; Down and Steel, 1983), but appear quite similar to man in sensitivity.

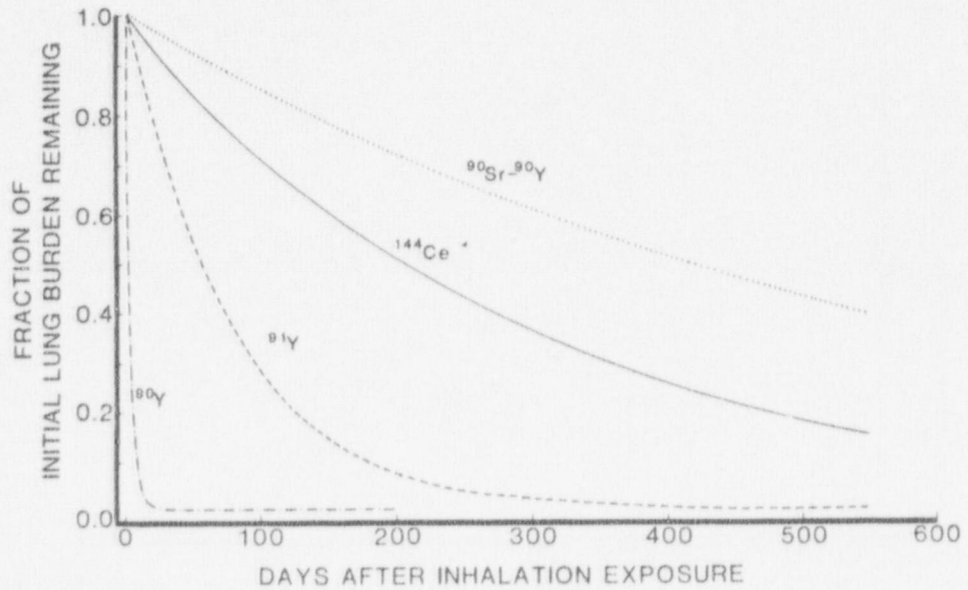

Figure 3.3 Normalized patterns of retention of radioactivity in the lungs of dogs after single inhalation exposure to the beta emitters ^{90}Y, ^{91}Y, ^{144}Ce, or ^{90}Sr (in equilibrium with daughter ^{90}Y) inhaled in an insoluble form (McClellan et al., 1982).

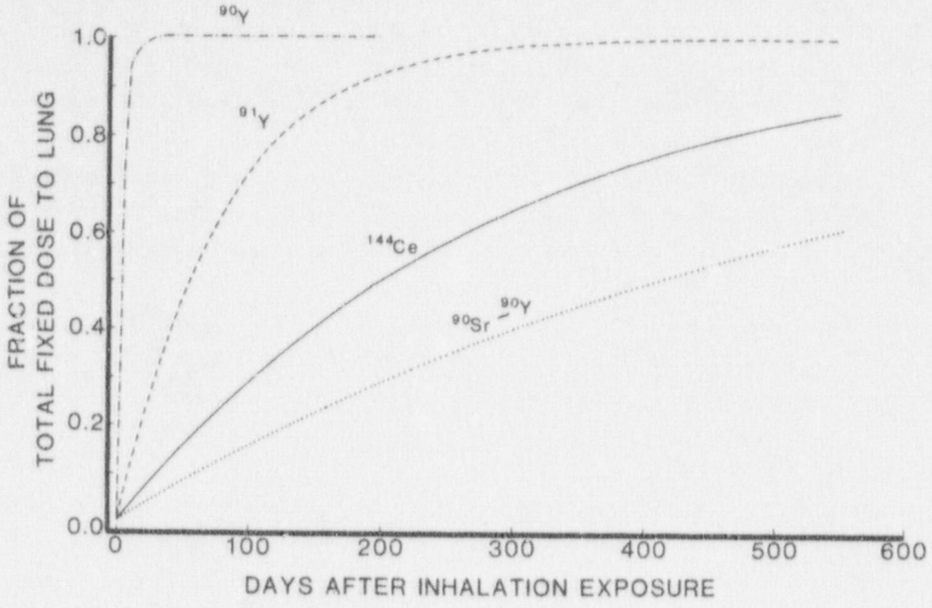

Figure 3.4 Normalized patterns of radiation dose accumulation in the lungs of dogs after inhalation exposure to beta emitters based on the retention curves shown in Figure 3.3 (McClellan et al., 1982).

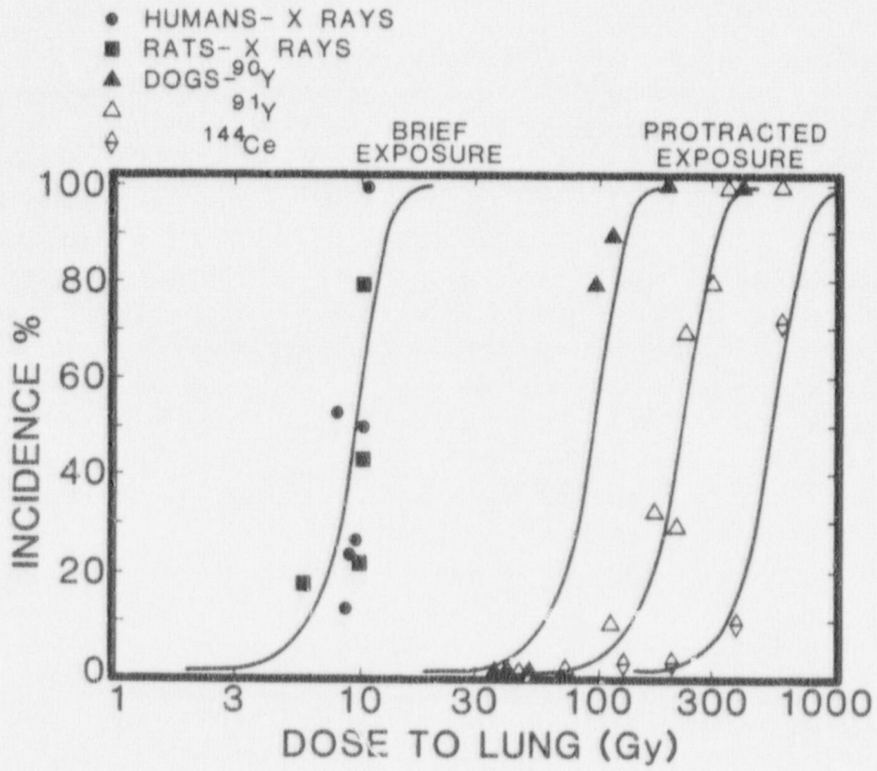

Figure 3.5 Dose-response curves for death from radiation pneumonitis and/or pulmonary fibrosis after inhalation exposure of dogs to ^{90}Y, ^{91}Y, or ^{144}Ce inhaled in an insoluble form (Scott and Hahn, 1989; Scott and Seiler, 1984). Also shown are dose-response curves for the incidence of death from early effects after brief upper-body X irradiation of rats (Dunjic et al., 1960), and for radiation pneumonitis in man after brief thoracic photon irradiation (Van Dyk et al., 1981).

The radionuclide-exposure data in Figure 3.5 are based on use of the 1-year dose to the lung as the independent variable, with all deaths from radiation pneumonitis being counted and deaths from competing risks being eliminated (Scott and Seiler, 1984). Most of the deaths occurred within 1.5 years of the inhalation exposure. For the external exposure data for rats and man, the cumulative absorbed radiation dose to the lung was used.

The 1-year dose was selected as the independent variable for the radionuclide data, since for a given pattern of irradiation, it can be calculated before an animal dies from radiation-induced effects. Dose to 1.5 years or some other reasonable time could also have been selected alternatively.

Dose to a fixed time (time-specific dose) is recommended as a predictor variable in risk assessment associated with chronic irradiation by internally deposited radionuclides (Scott et al., 1987; Filipy et al., 1988). In this report, the time-specific, 1-year dose is designated as DOSE-1y; dose to other times can be indicated in a similar way (e.g., the time-specific 6-month dose can be designated as DOSE-6mon).

An influence of beta dose-rate pattern similar to that observed for dogs was also observed in rats when the frequency of deaths from RPPF was evaluated as a function of the DOSE-1y (Scott et al., 1987). Rats inhaled equilibrium or nonequilibrium mixtures of ^{90}Y plus ^{90}Sr, in fused aluminosilicate particles, to provide different patterns of irradiation of the lung. As in the studies with dogs (McClellan et al., 1982), the D_{50} increased as the exposure time increased. In Chapter 4, a dose-response model is presented that has been demonstrated to predict the median lethal doses for the rat studies, solely based on information about the dose-accumulation patterns. Parameters for the model are based on the data for dogs shown in Figure 3.5 (Scott et al., 1987).

Pulmonary function data have been quantified in the following way to develop risk parameters for estimating the prevalence or respiratory dysfunction resulting from irradiation of the lung of rats or dogs (Scott et al., 1987, 1988b; Filipy et al., 1988, 1989). Irradiated individuals having a vital capacity measurement less than the lower 95% confidence interval for unirradiated controls were judged to have a reduced lung volume. Those having a CO diffusing capacity less than the lower 95% confidence interval for controls were judged to have abnormal gas exchange. Those having a quasistatic compliance less than the lower 95% confidence interval for controls were judged to have stiffer than normal lungs. Those having a slope of phase 3 of the N_2 washout curve greater than the upper 95% confidence interval for controls were judged to have an abnormal ventilation distribution. Individuals having three or more abnormal values for the four mentioned parameters were judged to have respiratory functional morbidity (Scott et al., 1987, 1988b; Filipy et al., 1988, 1989).

Dose-response data for respiratory functional morbidity after internal high- or low-energy beta irradiation of the lung are provided in other publications (Scott et al., 1987, 1988b; Filipy et al., 1988). Data are also available for combined external-gamma (total-body) and internal-alpha irradiation of the lung (Filipy et al., 1988).

In studies at the IITRI using internally deposited high-energy beta-emitting radionuclides (^{90}Y + 2.3% ^{90}Sr, ^{90}Y + 25% ^{90}Sr, or ^{90}Sr in equilibrium with ^{90}Y), the dose D_{50} required to produce respiratory functional morbidity in 50% of those exposed was about the same as was required for lethality from RPPF (Scott et al., 1987). The notations 2.3% ^{90}Sr or 25% ^{90}Sr implies that 2.3% or 25% of the initial lung burden was due to ^{90}Sr and the remainder was due to ^{90}Y. Because of smaller sample sizes, the morbidity data were more variable than the mortality data, and a lower D_{50} for morbidity could not be ruled out. For the low-energy beta emitter ^{147}Pm, the D_{50} for respiratory functional morbidity was about 25% of the D_{50} for death from RPPF (Scott et al., 1987). In a similar ^{147}Pm inhalation exposure study conducted in rats at Pacific

Northwest Laboratory (PNL), the D_{50} for respiratory functional morbidity was about the same as for lethality from RPPF (Filipy et al., 1989). Similar D_{50} values for mortality and morbidity were obtained at PNL when rats also received a sublethal external gamma-ray dose before internal beta irradiation by inhaled ^{147}Pm.

3.3.2.2 Lethality and Morbidity After Alpha Irradiation

In experiments at PNL, sublethal doses of total-body gamma followed by inhalation exposure to plutonium aerosols increased the lethality from all causes in both Beagle dogs and F344 rats. The lung DOSE-ly of plutonium that led to 50% mortality when given in combination with gamma irradiation was approximately one-half that led to 50% mortality from plutonium alone. The data indicated that the enhancement effect due to external gamma irradiation was greater in dogs than in rats (Filipy et al., 1988), owing to a higher sensitivity of dogs to deaths from injury to the hematopoietic system. However, respiratory functional morbidity resulting from inhaled plutonium was enhanced to a much lesser extent by total-body gamma irradiation than was lethality.

Lung doses from plutonium that were expected to lead to 50% mortality within a year of inhalation exposure resulted in 100% mortality in F344 rats following a sublethal exposure to gamma rays (Filipy et al., 1988). With dogs, a 235 rad (2.35 Gy) total-body gamma dose reduced the D_{50} for 1-year lethality from all causes from 4500 rad (45 Gy) to 2000 rad (20 Gy), indicating a reduction of 2500 rad (25 Gy) in the plutonium dose. The reduction is not surprising, since a brief exposure to 235 rad is very near to the LD_{50} for the hematopoietic mode of death (LD_{50} = 243 rad, Filipy et al., 1988).

The threshold for the hematopoietic mode of death is estimated to be about 1/2 of the LD_{50} (Scott and Hahn, 1988), which puts it at about 122 rad (1.22 Gy). Based on a recent acute lethality model for death from the hematopoietic mode (Scott et al., 1988a), 235 rad (2.35 Gy) of gamma rays uniformly distributed to the bone marrow of dogs and delivered at high dose rates would be expected to lead to about 40% lethality from injury to the bone marrow for large sample sizes. For a small sample (e.g., 10 or less) selected at random, the lethality could exceed 60% because of statistical fluctuations.

The results suggest a relative effectiveness of 2500/235 ≈ 11 for the high dose rate, total-body gammas exposure, relative to protracted alpha irradiation of the lung of dogs for 1-year lethality. However, a large part of this relative effectiveness factor of 11 is likely due to deaths from the hematopoietic mode, rather than to a synergistic interaction between the lung and bone marrow because the 235 rad gamma dose is close to the LD_{50} of 243 rad for hematopoietic death.

Respiratory functional morbidity was also measured in the study with dogs, and the data indicated a relative effectiveness factor of 1.1 for total-body gamma irradiation vs internal alpha irradiation of the lung (Filipy et al., 1988). Because of the small sample sizes used, the error on the relative effectiveness factor of 1.1 may be quite large.

Acute lethality data for F344 rats receiving a dose of gamma rays followed by inhalation exposure to $^{239}PuO_2$, provide additional information on the relative effectiveness of external gamma-ray, total-body exposure, relative to internal alpha irradiation of the lung (Filipy et al., 1988). In the rat study, a D_{50} plutonium lung dose of 5800 rad (58 Gy) for 1-year lethality was reduced to 3600 rad (36 Gy) when combined with total-body ^{60}Co gamma doses of 850 to 915 rad (8.5-9.15 Gy) (midrange 883 rad, 8.83 Gy); corrections were made for deaths from the hematopoietic mode by excluding animals that died within 30 days. Dose-response curves for 1-year lethality are given in Figures 3.6-3.7.

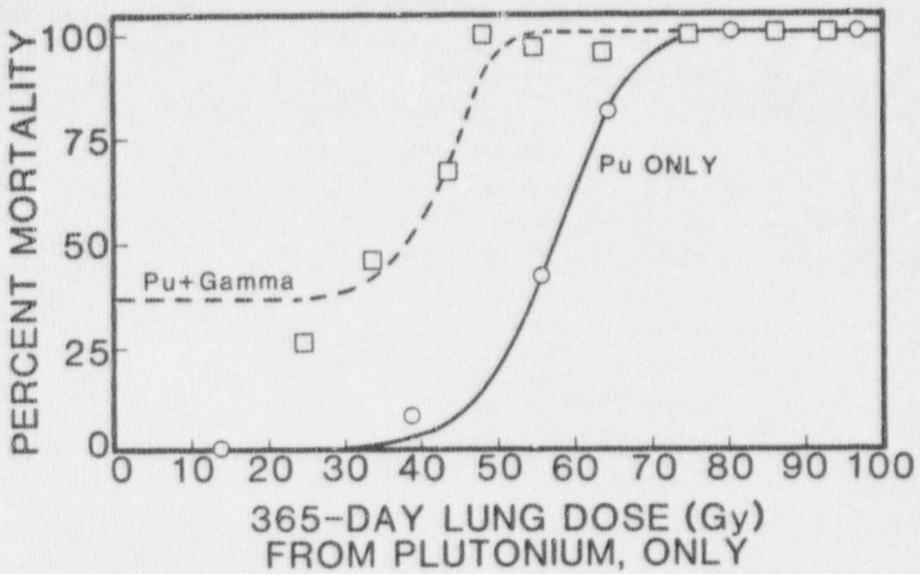

Figure 3.6 Percent mortality after inhalation exposure of male and female rats to $^{239}PuO_2$ only or in combination with a conditioning dose (850-915 rad, 8.5-9.15 Gy) of external ^{60}Co gamma rays. No adjustments for 30 day lethality from injury to the bone marrow were made (Filipy et al., 1988).

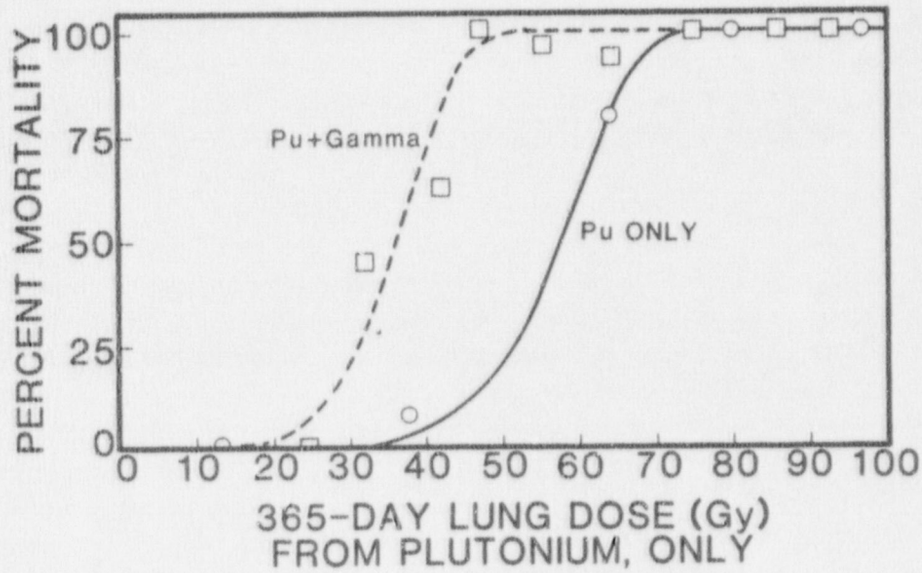

Figure 3.7 Percent mortality after inhalation exposure of male and female rats to $^{239}PuO_2$ only or in combination with a conditioning dose (850-915 rad, 8.5-9.15 Gy) of external ^{60}Co gamma rays. Rats dying within 30 days from injury to the hematopoietic system were excluded.

The experimental design of the study, in particular its 1-year duration, did not allow us to determine whether the reduction in the alpha D_{50} for 1-year lethality after combined alpha plus gamma irradiation was due to an increase in the risk of death from RPPF. Had the rats exposed to alpha-only been followed for duration of life, we would expect the D_{50} for that study to approach the D_{50} for the alpha-plus-gamma study. Results of analysis of survival time distribution data

suggests that sublethal total-body gamma doses may have accelerated the development of lethal lesions induced in the lung by chronic alpha irradiation.

The observation of a D_{50} of 3600 rad (36 Gy) for 1-year lethality, for the combined alpha-plus-gamma study in rats, is consistent with the D_{50} for 3-year lethality from RPPF observed in dogs exposed via inhalation to $^{239}PuO_2$ at the ITRI. In the dog study, the D_{50} (expressed as a 3-year dose to the lung) was approximately 3500 rad (35 Gy) for death from RPPF (Scott et al., 1986).

The results of the PNL alpha plus gamma study in rats suggest a relative effectiveness of (5800-3600)/[883] = 2.5 for the high dose rate total-body gamma exposure, relative to protracted alphas (based on a 1-year dose and 1-year lethality). This means that for irradiation of the lung only, with external gamma photons, the D_{50} for RPPF would be expected to be equal to about (D_{50} for alphas only)/2.5, if synergism between injury to the lung and bone marrow did not occur in the combined exposure. Assuming the D_{50} for alphas to be about 3500 rad (35 Gy), the D_{50} for external gammas for death from RPPF is estimated to be about 3500 rad/2.5 = 1400 rad (14 Gy).

The 1400 rad (14 Gy) estimate is in good agreement with adjusted values of 1500 rad (15 Gy) and 1700 rad (17 Gy) derived, respectively, from data for thoracic 300 kVp (Cardozo et al., 1985) and 280 kVp (Kurohara and Casarett, 1972) X-ray irradiation of rats. We have made adjustments for a lesser effectiveness for gamma rays as compared to low-energy X rays, based on an RBE of 0.87 for the gammas (MacVittie et al., 1984). Also, the X-ray data in Figure 3.5 when adjusted for LET effects using the factor 0.87, would place the D_{50} at about 1100 rad (11 Gy) to the lung for high-energy photons.

Published estimates for the D_{50} for external thoracic photon irradiation of mice were in the range 1100-1500 rad, when no drugs were used and when radiation pneumonitis was confirmed (Dunjic et al., 1960; Cardozo et al., 1985; Down and Steel, 1983). Together, the results from thoracic exposure studies in rats and mice would place the D_{50} for death from RPPF at about 1300 rad to the lung for gamma radiation.

Experiments were conducted to study the incidence of death from RPPF after simultaneous internal alpha (^{238}Pu) and beta (^{147}Pm) irradiation of the lung of rats (Scott et al., 1988b). The radionuclides were inhaled in an insoluble fused aluminosilicate particle matrix. The normalized alpha and beta doses (i.e., DOSE-ly divided by the D_{50}) were found to be additive for simultaneous exposure as is predicted by the hazard-function model (see Chapter 4). Additivity of normalized doses, however, does not imply independent action (Scott, 1989).

A response-surface for lethality from RPPF after the combined (simultaneous) alpha and beta irradiation of the lung based on the hazard function model is given in Figure 3.8 (Scott et al., 1988b). Results were presumed to be applicable to both low-energy and high-energy betas as the D_{50} for lethality from RPPF does not seem to depend on beta energy for maximum beta energies in the range of 0.224-2.27 MeV (Scott et al., 1987).

Respiratory functional morbidity was also examined in rats after combined simultaneous ^{238}Pu-alpha plus ^{147}Pm-beta irradiation of the lung (Scott et al., 1988b). The normalized alpha and beta doses were found to be additive as predicted by the hazard-function model (Scott et al., 1988b) discussed in Chapter 4. A response-surface model obtained for respiratory functional morbidity after the combined alpha and low-energy beta irradiation of the lung is given in Figure 3.9. The results indicated that the D_{50} for the prevalence of morbidity was about 1/4 of that required for lethality from RPPF. This can be seen by comparing the marginal curves on the two response surfaces in Figures 3.8 and 3.9.

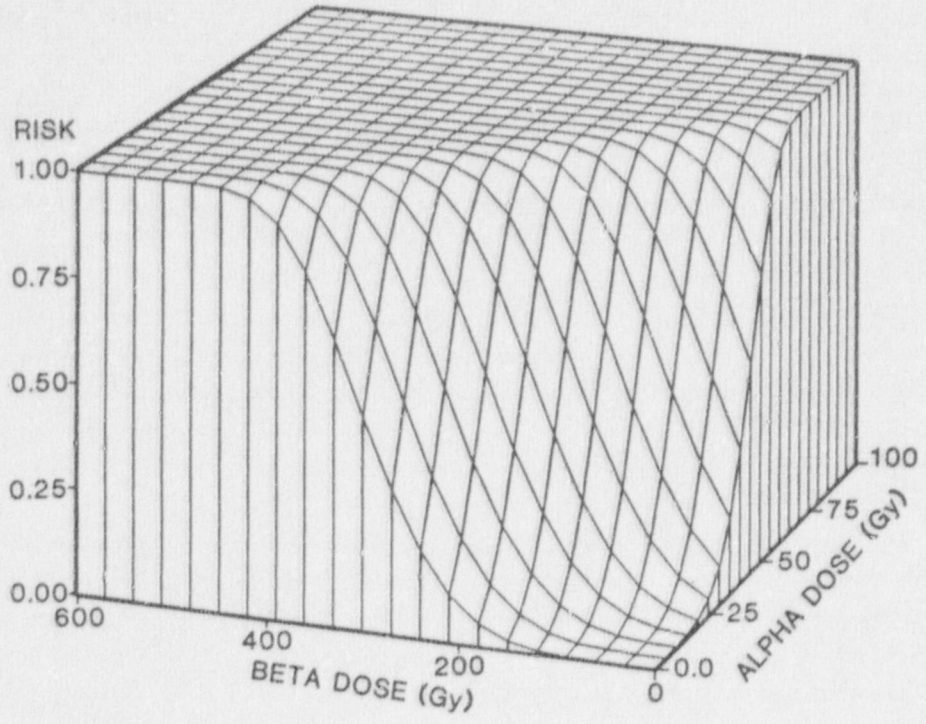

Figure 3.8 Response-surface for the estimated risk of death from RPPF after chronic internal ^{238}Pu alpha + ^{147}Pm beta irradiation of the lung, based on studies in rats (Scott et al., 1988b). Results are presumed to be applicable to man when the radionuclides are inhaled in an insoluble form.

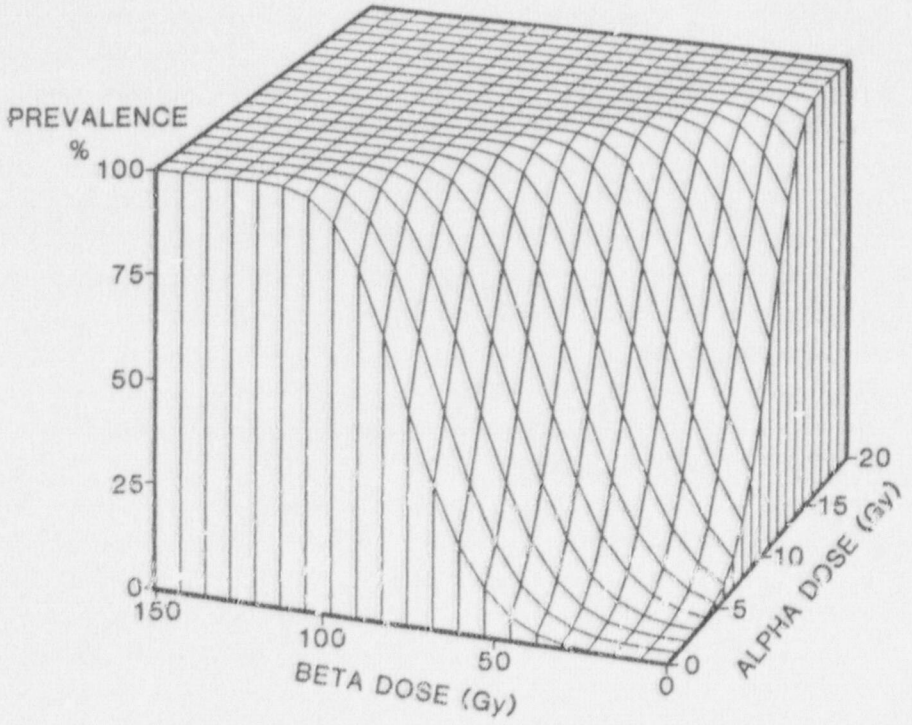

Figure 3.9 Response-surface for the estimated prevalence of respiratory functional morbidity after combined internal ^{238}Pu alpha + ^{147}Pm beta irradiation of the lung, based on studies in rats (Scott et al., 1988b).

CHAPTER 4
HEALTH EFFECTS MODELS FOR LUNG

4.1 EFFECT OF MODEL SELECTION

A number of models were considered for predicting lethality or morbidity from irradiation of the lung. However, because of the steepness of the sigmoidal dose-response relationships (Scott et al., 1987; Scott and Hahn, 1989; Scott, 1980), the choice of a dose-response model is not as crucial as one might expect. Almost any plausible sigmoidal-type function would lead to about the same number of expected deaths, for most nuclear accident scenarios of interest. A two-parameter Weibull model was selected. Other models were considered (Jones, 1981; Goldman and Peabe, 1977; Wells, 1976; Filipy et al., 1980; Morris and Jones, 1988), including the tolerance-dose-distribution models (logit, gamma, extreme value, linear probit, log-normal).

When modeling acute lethality from injury to the bone marrow after a brief exposure, the linear probit and logit model may actually perform better in the very low and very high risk regions than the two-parameter Weibull model (Morris and Jones, 1988). However, the two-parameter Weibull model is easy to implement, and when based on the normalized dose, has certain advantages in accounting for dose-rate effects and linear-energy-transfer (Scott et al., 1987, 1988a, 1988b).

A shortcoming of all of the models cited is that none incorporate absolute thresholds. However, thresholds can be handled by truncation (i.e., defining the risk to zero), as indicated in Section 4.7, when dose is below a specified value. Meticulous individuals concerned about performance of the two-parameter Weibull model in the very low and very high risk regions may prefer to use the three-parameter Weibull model. However, we feel that the two-parameter Weibull model is adequate for modeling early and continuing effects of nuclear accidents where one is concerned about effects of (1) a distribution of dose over the hypothetical target population, (2) different doses to different critical organs in the body, and (3) brief, external gamma exposure plus protracted, internal alpha, beta and gamma exposure.

Uncertainty in dose and dose rate pattern for a given accident will contribute a much larger error in a risk assessment than a relatively small systematic error associated with use of the two-parameter Weibull model. For a population exposed to gamma radiation from a passing radioactive cloud (cloud-shine) and contaminated ground surface (ground-shine), and which also inhaled varying amounts of alpha-, beta-, and gamma-emitting radionuclides, errors associated with radiation doses to each critical organ (e.g., bone marrow, lung, small intestine, skin, thyroid, and etc.) of each exposed individual and errors associated with the dose-rate patterns could be very large. For early effects risks, the average absorbed dose and average dose-rate pattern (organ-specific) for the population cannot be used in estimating risk, because of the usual threshold and sigmoidal characteristics of the risks. One has to determine the average risk as a function of the distribution of absorbed dose and absorbed dose rate pattern over the population (Evans et al., 1985; Scott, 1988a).

The following section summarizes the special form of the two-parameter Weibull model that was developed for modeling tolerance-dose distributions for lethality or morbidity from early effects of irradiation. It also introduces the reader to the cumulative hazard function which plays a central role in our modeling of risk for early and continuing effects of irradiation.

4.2 TOLERANCE DISTRIBUTION MODELING

Tolerance dose represents that dose to a given individual, and to the critical organ of interest, that is just sufficient to cause the quantal effect of interest (e.g., death from RPPF in lung). Sensitive individuals will have lower tolerance doses than resistant individuals. For a large population at risk, there is a distribution of tolerance doses. When the linear probit or

log probit model is used to develop dose-effect relationships, it is implied that a normal or log-normal tolerance distribution has been assumed, respectively. For quantal effects of irradiation such as lethality from RPPF, the tolerance dose will depend on a number of variables, including the type of radiation and the temporal pattern of irradiation.

We have assumed that the population at risk is sufficiently large that the distribution of tolerance doses can be approximated by a continuous function, that the critical organ of interest is uniformly irradiated, and that no supportive or intensive medical treatment is provided to the exposed individual.

Three mathematical concepts from probability theory play important roles in radiation tolerance dose distribution modeling: (1) the cumulative distribution function (cdf); (2) the survival function (sf); and, (3) the cumulative hazard function (chf). The cdf represents the proportion of the population at risk that will respond (e.g., die from a specific early effect of irradiation), when each member is exposed in the same way, to the same dose of a specific type of radiation. The cdf is related to the tolerance distribution. In risk assessment, the cdf is estimated using what is often called the risk function.

The tolerance distribution for cumulative absorbed doses D is estimated by the estimator function f(D|pattern, type), where the notation implies that, in addition to depending on organ dose D, the temporal pattern of irradiation and the type of radiation (i.e., radiation quality) are also important. The fraction of the population with tolerance doses in the infinitesimal interval (D, D + dD) is given by the product fdD, where for simplicity, f has replaced the more complicated notation f(D|pattern, type). However, it should be understood that the conditional relationship and dose dependence exist. Tolerance distribution can also be expressed in terms of the normalized dose X (Scott, 1988a, 1988b, 1989).

4.3 WEIBULL HAZARD-FUNCTION ESTIMATOR

For lethality from radiation-induced injury to the lung, the cumulative hazard is called the lethality hazard; for morbidity, it is called the morbidity hazard. We use H to represent an estimator function for the lethality or morbidity hazard. The general expression that we have used for H is based on the Weibull model (Scott et al., 1987, 1988a, 1988b) where

$$H = \ln(2)(D/D_{50})^V = \ln(2)x^V, \qquad (4.1)$$

where D is the absorbed radiation dose, D_{50} is that dose which produces the effect of interest in 50% of those exposed, and V is a parameter (shape parameter) that determines the shape of the dose-response curve. Equations are provided in Appendix B for estimating the shape parameter for simultaneous exposure to different types of radiation. For lethality, D_{50} represents the median lethal dose; for morbidity, it represents the median effective dose. From Eq. 4.1 it can be seen that when the dose D equals the D_{50}, H will be equal to ln(2) which is approximately 0.693. Because of Eq. 4.1, a plot of H vs D can be used to estimate the D_{50} (Scott, 1988a).

For acute effects of irradiation, data for H vs the dose D is usually a straight line (Scott and Hahn, 1980) when plotted on logarithmic paper, and when the two-parameter Weibull model is used to fit the data for H, the fitted curve for H passes through the value 0.693 at the dose D_{50}. Also, the slope of the curve will indicate the model shape parameter V. Linear regression of ln(H) vs ln(D) is one way to estimate the shape parameter V.

The maximum likelihood procedure (based on risk, not hazard) provides a second way to estimate the shape parameter V. With the maximum likelihood procedure, individuals with different doses do not have to be grouped, but can be analyzed separately (Scott et al., 1987).

The shape parameter can also be estimated with a calculator from a plot of incidence of effect vs dose relationships. If D_{10} and D_{90} are doses for 10% and 90% incidences, respectively, then an estimate of the shape parameter V is $3.084/\ln(D_{90}/D_{10})$.

The parameters D_{50} and V depend on the biological effect of interest and the type of radiation (Scott et al., 1987; Scott and Hahn, 1989; Filipy et al., 1988, 1989). While the D_{50} for acute lethality from a specific mode depends strongly on low-LET dose rate, the shape parameter V seems not to depend on dose rate (Scott et al., 1987, 1988a).

With the modeling approach used, one first obtains the lethality or morbidity hazard estimator function H. The corresponding lethality or morbidity risk estimator function is then obtained as a function of H. Details on how to obtain the risk estimator function R from H are provided in Section 4.5.

4.4 NORMALIZED DOSE X

The ratio D/D_{50} in Eq. 4.1 can be viewed as representing a normalized dose X in units of the D_{50}. Like the dose equivalent, the dose X is theoretical. Unlike the dose equivalent, the dose X is dimensionless. For lethality, X = 1 corresponds to the median lethal dose, regardless of the type of radiation or dose rate pattern; X = 0.5 corresponds to one-half of the median lethal dose. Advantages of using the normalized dose X instead of the absorbed dose D in the analysis of data for early effects of irradiation have previously been demonstrated (Scott et al., 1987, 1988a, 1988b; Scott, 1988a, 1988b; Jones, 1981). Use of X instead of D eliminates variability in dose-response relationships associated with different mammalian species (Scott et al., 1988a), with differences in radiation quality (Jones, 1981), and with differences in dose rate (Scott et al., 1988a). The data in Figures 3.1 and 3.2 in Chapter 3 were plotted as functions of the normalized dose X.

Because of the complex irradiation patterns that could occur following a nuclear power plant accident, use of the normalized dose method to evaluate risk is preferable to use of the dose-equivalent method. With the dose-equivalent method one multiplies the "total absorbed radiation dose" by a fixed quality factor to obtain a theoretical dose equivalent in rem (or Sv), where this theoretical dose represents an equivalent effects scale. On this theoretical dose scale, 100 rem of dose of any radiation, delivered at any fixed dose rate, would be expected to produce the same effect.

The dose-equivalent approach was intended for cases where the dose rate is fixed and the dose-response curve is linear; for inhalation exposure to radionuclides following a nuclear power plant accident, exponentially decaying pattens of irradiation of the lung could occur and acute effects dose-response curves are nonlinear. In such cases, each small increment in the radiation dose is delivered at a different dose rate. The dose-equivalent approach was not intended for predicting the effects of such complex patterns of irradiation. For this and other reasons, the normalized dose was developed. Use of the normalized dose X facilitates prediction of the acute effects of exponentially decaying and more complex patterns of low-LET irradiation of a target organ. Unlike the dose-equivalent approach, use of the normalized dose X allows one to treat "each small increment" in the dose differently to account for effects of a changing dose rate pattern. We show in Section 4.8 how its use also allows one to treat dose-rate and LET effects simultaneously.

4.5 RISK FUNCTION ESTIMATOR

The risk estimator for morbidity or lethality is related to the hazard estimator H, and tolerance dose distribution estimator f, by the expression:

$$\text{Risk } R \text{ at absorbed dose } u = 1 - \exp[-H] = \int_0^u f\,dD, \tag{4.2}$$

where f is the tolerance dose distribution estimator function. Both H and f depend on D, on the pattern of irradiation, and on the type of radiation. Thus, the risk estimator function will also depend on these variables. It follows from Eq. 4.2 that errors in risk estimates will depend on error in H, which in turn will depend on errors in the critical organ dose and the dose-response model used for H.

For threshold-type effects, with sigmoidal-type risk functions, an estimate of the average risk is needed for a population with a distribution of organ-specific doses. For sigmoidal-type curves, one cannot use the average dose to the population to evaluate risk; use of the average dose is restricted to linear nonthreshold effects.

After the average risk has been estimated, multiplying it by the size of the group of people exposed gives the central estimate, in the absence of competing risks of the expected cases of a given effect. Usirg the hazard-function approach, competing risks can also be incorporated in the overall risk evaluation quite easily (Scott and Hahn, 1985, 1989).

4.6 SURVIVAL FUNCTION ESTIMATOR

The survival function estimator is related to the hazard function estimator H by

$$\text{Survival } S \text{ at dose } u = 1 - (\text{Risk } R) = \exp[-H] = \int_u^\infty f\,dD. \tag{4.3}$$

It follows from Eq. 4.3 that

$$H = -\ln[S] = -\ln[1-R]. \tag{4.4}$$

4.7 THRESHOLD DOSE

The threshold dose is the smallest tolerance dose for the population at risk and specific nonstochastic quantal effect of interest. Threshold doses can easily be simulated with the two-parameter Weibull model, by using the truncation method. With the truncation method, the hazard function estimator H is allowed to take on a nonzero value only if the total normalized dose X to the critical organ of interest exceeds the threshold dose X_0. While the exact threshold dose X_0 is generally not known, one can obtain a practical threshold by plotting ln(X) vs ln(H) for most acute quantal effects. In a previous publication (Scott, 1988a), a similar approach was used to estimate effective absorbed dose thresholds for different early effects of irradiation. Dividing the threshold, expressed as an absorbed dose, by the D_{50} also gives an estimate of X_0.

Truncation of H to simulate a threshold dose will lead to a discontinuity in the dose-effect relationship for R at the dose of truncation. However, this should pose no major problem in nuclear accident risk assessment so long as its use is limited to threshold-type effects and is applied to situations where there is a distribution of doses over the population of interest. In such situations, the probability of having a dose in the very small dose interval (X_0 - c, X_0 + c), which is centered at the discontinuity, where c is a small number like 0.1, will be much smaller than the probability that the dose will be outside the interval. Because the number of expected number of cases of a given effect is based on the average risk (which depends on the risk at a given dose multiplied by the probability of having that dose, for all doses), the impact of

the discontinuity would be expected to be negligible. This is because the contribution to the average risk coming from the small dose interval ($X_0 - c$, $X_0 + c$) will be minor for realistic nuclear accident scenarios.

4.8 INTERORGAN INTERACTIONS

Total-body exposure to sublethal external photon doses in combination with internal irradiation of the lung from inhaled radionuclides could lead to interaction between bone marrow and lung (Filipy et al., 1988, 1989). Such an interaction effect can easily be represented by using hazard function estimators and normalized doses. Throughout the remainder of the document, hazard function estimators will be called hazard functions; similarly, risk function estimators will be called risk functions.

We first treat the relatively simple case of combined brief exposure to sublethal external gammas (total-body irradiation), followed immediately by chronic, alpha irradiation of the lung. We then show how to add in chronic, beta and gamma irradiation from internally deposited radionuclides.

The hazard-function model for brief, external gammas followed by chronic internal alpha irradiation of the lung is represented by the following equation (where L and B imply lung and bone marrow, respectively):

$$\begin{aligned}\text{Overall hazard } HL(XL_a, XL_g, XB_g) = \\ \text{hazard due to alpha and gamma irradiation of the lung } HL(XL_a, XL_g) \\ + \\ \text{hazard due to interaction between the lung and bone marrow } HLB(XL_a, XL_g, XB_g),\end{aligned} \tag{4.5}$$

where XL_a and XL_g are normalized alpha and gamma doses to the lung, respectively, and XB_g is the normalized external gamma dose to the bone marrow, for uniform total-body exposure. Results of studies at PNL presented in Chapter 3 indicated that the interorgan, interaction hazard HLB can be neglected when nonlethal external photon doses are given to the bone marrow, provided that lifetime risk is the endpoint of interest. The results suggest that the main influence of nonlethal, external gamma photons in the combined exposure was to cause earlier death from alpha-induced RPPF, rather than an increased number of deaths over what would be expected with only alpha irradiation. Thus, for combined exposure to a sublethal, external gamma dose XB_g to the bone marrow, an external gamma dose XL_g to the lung, and an internal alpha dose XL_a to the lung, the hazard function for lethality or morbidity effects in the lung should be adequately represented by

$$HL(XL_a, XL_g, XB_g) = HL(XL_a, XL_g). \tag{4.6}$$

The solution to Eq. 4.6 is given in terms of the isoeffect dose XL_a^* and the alpha dose XL_a where XL_a^* is the alpha dose that would produce the same level of hazard (or risk) as the external gamma dose XL_g. The solution (Scott, 1984; Hahn, 1979) is

$$HL(XL_a, HL_g) = HL_a(XL_a + XL_a^*), \tag{4.7}$$

where HL_a is the hazard function when the individual is exposed only to alpha radiation evaluated using Eq. 4.1 (Scott et al., 1984), and where the isoeffect dose is the solution to the equation

$$HL_a(XL_a^*) = HL_g(XL_g). \tag{4.8}$$

where HL_g is the hazard function when the lung is exposed only to external gamma rays. By changing each subscript a in Eq. 4.8 to b, one could also define an isoeffect dose to XL_b^*. Both $HL_a(XL_a^*)$ and $HL_g(XL_g)$ are evaluated using Eq. 4.1, with appropriate model parameters for alpha and external gamma irradiation.

Results obtained from a study at the ITRI indicated that normalized, internal alpha- and beta-doses XL_a and XL_b are additive for both lethality from RPPF and for respiratory functional morbidity (Scott et al., 1988b). Additivity was expected, based on the hazard-function model, since the shape parameter V for the Weibull dose-response model was approximately the same for internal alpha and beta irradiation of the lung (V = 5), for both lethality from RPPF and for morbidity. This means that the hazard function for morbidity or for lethality from effects of external gamma + internal alpha + internal beta and gamma irradiation of the lung should be adequately estimated using HL_a $(XL_b + XL_a + XL_a^*)$, which is the same as $HL_b(XL_b + XL_a + XL_a^*)$, where XL_a^* accounts for the effects of the high dose-rate, external gammas; HL_a and HL_b are the hazard functions for morbidity or lethality when the lung is exposed only to internal alphas, and to betas and gammas, respectively; XL_b is the normalized, internal beta + gamma dose to the lung, with internal betas and gammas being assumed equally effective (Scott and Hahn, 1985, 1989). Since the shape parameter is the same for alpha and beta irradiation, no calculation of an isoeffect dose is needed for internal betas and gammas.

The much greater effectiveness of brief, external gamma irradiation, compared to protracted internal alpha or beta irradiation, is presumed to be due to dose rate. However, brief exposure to alpha particles would be expected to be more effective than brief exposure to external gammas. For this reason, the results presented are considered applicable only to chronic alpha irradiation. A plot of the lethality hazard HL (as estimated by HL_a), as a function of the total dose XL, where $XL = XL_b + XL_a + XL_a^*$, is given in Figure 4.1.

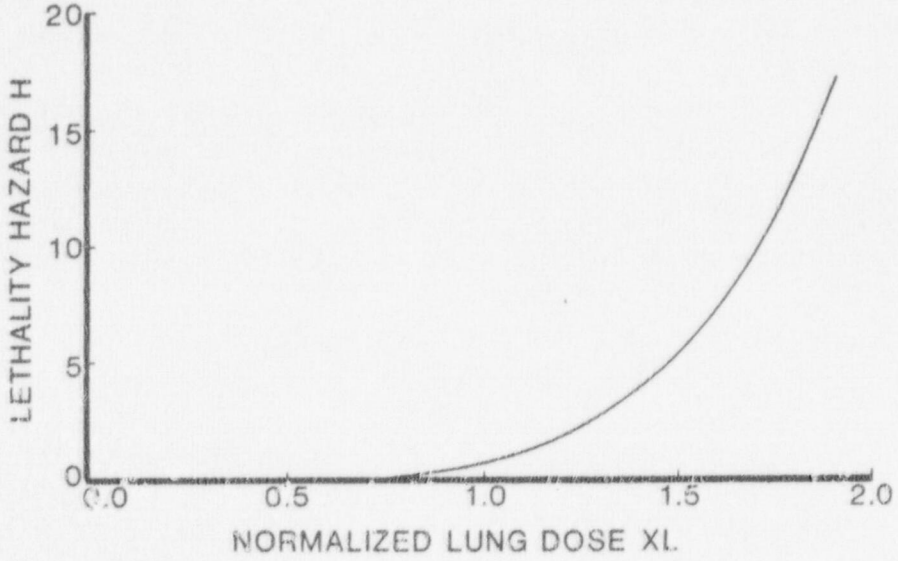

Figure 4.1 Lethality hazard for death from RPPF as a function of the total normalized dose XL to the lung, where $XL = XL_b + XL_a + XL_a^*$.

For lethality in man from RPPF, the dose XL_b is evaluated using the same fixed parameter model for effects of beta irradiation of the lung, as previously published (see following section). The normalized alpha dose XL_a is presently calculated as D/3500, when the total

cumulative absorbed alpha dose D is in rad. For alpha irradiation, the total alpha dose is used because of recent experimental results; these results indicate that unlike early effects of beta irradiation of the lung, which generally occur within 2 years during chronic exposure to exponentially decaying patterns (McClellan et al., 1982), there is evidence that RPPF can occur as late as 7 years while receiving chronic alpha irradiation (Muggenburg et al., 1988).

For external irradiation of the lung of man, the D_{50} for death from RPPF has been estimated to be 1000 rad (10 Gy) (Scott and Hahn, 1988), as compared to the 1300 rad (13 Gy) estimate obtained in Chapter 3 for rats and mice. This means that the normalized dose XL_g in Eq. 4.8 for external gamma irradiation of the lung of man has to be based on a D_{50} of 1000 rad for lethality from RPPF, rather than on 1300 rad. The shape parameter V for external gammas is estimated from the animal data in Figure 3. to be about 12 (Scott and Hahn, 1989) as compared to a value of 5 (Scott et al., 1987, 1988b) for internal alpha or beta irradiation. A judgmental estimate of the threshold dose is $X_o = 0.5$ (Scott and Hahn, 1989).

The isoeffect dose (the solution to Eq. 4.8), is given by the solution to

$$XL_a{}^{*5} = XL_g{}^{12}$$

or

$$XL_a{}^{*} = XL_g{}^{2.4}. \qquad (4.9)$$

4.9 ESTIMATION OF XL_b

In the ideal case, the normalized beta dose is evaluated using the integral (Scott et al., 1988a; Scott and Hahn, 198

$$XL_b = \int \dot{D}*D_{50}(\dot{D})^{-1}\, dt, \qquad (4.10)$$

where the star (*) represents a product, and where the integration is over the time of exposure, for a continuous irradiation pattern; $\dot{D}$ is the instantaneous absorbed dose rate to the lung for both internal beta and gamma radiations; the normalization function $D_{50}(\dot{D})$ depends on the dose rate and represents the D_{50} as a function of the instantaneous dose rate. The normalization function $D_{50}(\dot{D})$ for man has been estimated from data for internal beta irradiation of the lungs of dogs (McClellan et al., 1982), for thoracic X irradiation of rats (Cardozo et al., 1985), for photon irradiation of the thorax of man (Van Dyk et al., 1981; Mah et al., 1987; Phillips and Margolis, 1972), and is given by the following relationship (see Appendix for full explanation):

$$D_{50}(\dot{D}) = [5170/\dot{D}] + 1000, \text{ in rad}, \qquad (4.11)$$

where the dose rate is in rad/min to the lung, and the D_{50} is in rad. When the dose rate is in Gy/hr, then the 5170 (in rad^2/min) should be replaced with 31 (in Gy^2/hr) and the 1000 (in rad) should be replaced with 10 Gy.

Whether an analytical solution to Eq. 4.10 exists depends on the problem considered. An analytical solution is provided in the Appendix for the special case where the dose rate to the lung decreases as a single negative exponential of the form A*exp[-B*t], where A is the initial dose rate to the lung, B is a positive parameter, and t is time. While the results are applicable to cases where the lung mass remains constant during the exposure, they may not apply to cases

where the lung mass increases significantly during the exposure, due to growth. For this reason, they are not applicable to our Phase II studies in rats (Scott et al., 1987).

For nuclear accident risk assessment, analytical solutions to Eq. 4.10 may be possible for some scenarios (e.g., exposure to external cloud- and ground-shine at a fixed dose rate, followed by chronic exposure to inhaled beta- and gamma-emitting radionuclides according to a single-exponential decaying pattern). However, searching for such solutions is beyond the scope of the current research project. Also, obtaining nearly exact numerical solutions for nuclear accident scenarios is not practical as computer time for population dose and dose-rate distributions could be sizable.

Two approaches to approximating the integral that do not require extensive computer calculations have been proposed for evaluating acute effects in lung: (1) the variable parameter approach, where the model parameter D_{50} changes for each of a number n of preselected time intervals, depending on the average dose rates in the interval; and, (2) the fixed-parameter approach (Scott et al., 1987; Scott and Hahn, 1985), where the model parameter D_{50} does not change with dose rate but differs for each of n (with n = 3) preselected time intervals.

While computer software for evaluation of the fixed-parameter model was developed as part of the research project, development of computer software for the variable-parameter model was beyond the scope of the project. Thus, only the fixed-parameter model has been used to predict results of experimental studies carried out in Phase II of this project. However, current research activities at Sandia National Laboratories will likely lead to incorporation of variable-parameter models for estimating the normalized doses for early effect in both the lung and bone marrow.

With the fixed-parameter approach, XL_b is estimated using the relationship

$$XL_b = D1/D_{50,1} + D2/D_{50,2} + D3/D_{50,3}, \qquad (4.12)$$

where D1 is the cumulative absorbed internal beta and gamma dose (in rad) to the lung that occurs during the 0-14 day interval following a nuclear accident; D2 is the dose that occurs during the 14-200 day time interval; and D3 is the dose that occurs in the 200-365 day interval. The normalization parameters $D_{50,1}$, $D_{50,2}$, and $D_{50,3}$ for death from RPPF are given, respectively, by 16,000 rad (160 Gy), 37,000 rad (370 Gy), and 92,000 rad (920 Gy), based on data in Figure 3.5 for chronic beta irradiation of the lung of dogs (Scott et al., 1987). A discussion of their derivation is provided in the reference cited.

The fixed-parameter model provides an easy way to predict the D_{50} in terms of the DOSE-ly in rad (or Gy). For a given exponentially decaying pattern (single or multiple components) of irradiation, with the fraction of the one-year dose to the lung that occurs in the 0-14 day interval given by f1, the fraction in the 14-200 day interval given by f2, and the fraction of the 200-365 day interval given by f3, the D_{50} is predicted using the reciprocal relationship (Scott et al., 1987)

$$1/D_{50} = f1/D_{50,1} + f2/D_{50,2} + f3/D_{50,3}. \qquad (4.13)$$

As shown in Table 4.1, model predictions are in good agreement with D_{50}'s obtained for death from RPPF after internal beta irradiation of the lung of rats for four studies conducted at the LRRI in Phase II of this project.

Table 4.1

Expected and Observed Median Lethal Doses for Death from Radiation Pneumonitis (Scott et al., 1987)[a]

Radionuclide	Fraction of 1-Year Dose			Normalized Fractions (Gy^{-1})			Sum of Normalized Fractions	n_{50} (1-Year Gy)[b]		
	f1	f2	f3	f1/160	f2/370	f3/920	(F)	Expected (1/F)	Observed	Observed / Expected
^{147}Pm	0.158	0.642	0.200	0.00099	0.00174	0.000217	0.00295	340	270	0.80
^{90}Sr	0.137	0.678	0.185	0.00086	0.00183	0.000201	0.00289	350	320	0.91
^{90}Y + 2.3% ^{90}Sr	0.758	0.188	0.054	0.00474	0.00051	0.000059	0.00531	190	190	1.0
^{90}Y + 25% ^{90}Sr	0.284	0.543	0.174	0.00178	0.00147	0.000188	0.00344	290	290	1.0

[a]Based on model $1/D_{50}$ = f1/160 + f2/370 + f3/920. See text for explanation.

[b]One Gray = 100 rad.

For respiratory functional morbidity, available data indicate that the normalization parameters in Eqs. 4.12 and 4.13 are in the range of 1 to 4 times smaller than normalization parameters for death from RPPF (Filipy et al., 1988, 1989; Scott et al., 1987, 1988b; Mauderly et al., 1973, 1980a), with an average of about a factor of 2 smaller. The available data on the shape parameter V for morbidity indicates no significant difference between the values for lethality from RPPF and for respiratory functional morbidity (Scott et al., 1987, 1988b; Filipy et al., 1988, 1989). Based on these results, we recommend that the same model that is used for lethality for death from RPPF also be used for respiratory functional morbidity, with all normalization parameters (for alpha, beta, and gamma radiations) being a factor of 2 times smaller for morbidity than for lethality. A factor of 2 was also used in the earlier version of the hazard-function model, which excluded alpha radiation (Scott and Hahn, 1985). An upper bound on the morbidity risk can be obtained by using a division factor of 4 and a lower bound by using a division factor of 1 (i.e., same as for lethality) to operate on the normalization parameters for lethality.

4.10 ISOBOLOGRAMS

The hazard-function model can be used to construct isobolograms for the combined effects of different radiations. An isobologram is a plot of dose combinations of two agents for a fixed level of effect. As an example, the hazard-function model has been used to predict combinations of external gamma doses and internal alpha doses to the lung of man for a 50% risk of death from RPPF. An isobologram at the 50% level (i.e., for the median lethal exposure) for death from RPPF for man, based on the hazard-function model, is given in Figure 4.2. In this example, the external gamma dose is delivered only to the lung. The isobologram is curvilinear when the absorbed dose is used. Also shown is an isobologram based on the assumption of independent action of the gamma and alpha radiation. The wide departure of the curve based on the hazard-function model from the curve based on the independent-action model implies that a dramatic synergistic effect is predicted by the hazard function model. The curvilinear relationship in Figure 4.2, based on the hazard-function model, indicates that the gamma and alpha doses in Gy are not additive in producing death from RPPF. That they are not additive is no surprise, as nonadditivity of high- and low-LET dose was the basis for development of the RBE concept.

A plot similar to that in Figure 4.2 is shown in Figure 4.3 based on the normalized gamma dose XL_g and normalized alpha dose XL_a. The results indicate that the normalized doses XL_a and XL_g are also not additive. Based on the hazard-function model, they would be expected to be additive only when the shape parameter V is identical for both radiations. However, the shape parameter for death from RPPF for gammas is 2.4 times larger than that for internal alphas.

As shown in Figure 4.4, if the isoeffect dose XL_a^* (i.e., the theoretical alpha dose that produces the same effect as the gamma dose) is used instead of XL_g (to account for the effects of the external gammas), a linear isobologram is obtained; a linear isobologram means that doses XL_a and XL_a^* are additive and is the basis for use of hazard-function models that depend on isoeffect doses (Scott, 1984).

In Figure 4.5, it is shown that the isobologram for 50% lethality from RPPF after combined chronic alpha and chronic beta irradiation of the lung is predicted to be linear when the normalized doses XL_a and XL_b are used. The linear relationship implies that XL_a and XL_b are additive, so that no isoeffect dose (e.g., XL_a^*) has to be calculated. The isoeffect dose is currently needed only when it is necessary to account for external gamma photons.

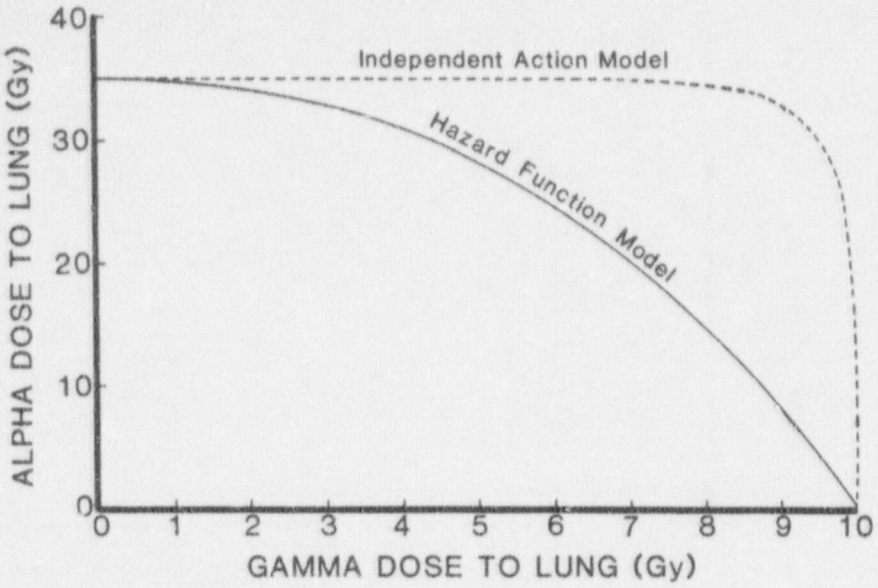

Figure 4.2 Isobologram at the median lethal exposure level for man when the lung is briefly exposed to external gamma rays followed by chronic internal alpha irradiation. Lethality within 1.5 years from RPPF is the biological endpoint modeled. The results show the combination of the total external dose (Gy) and the internal alpha dose (Gy) that would lead to a 50% chance of death from RPPF for 1.5 years of follow-up based on the independent-effects model and on the hazard-function model. If there were no synergistic effects, one would get the curve represented by the independent-effects model. Note that the hazard-function model predicts a very large synergistic interaction.

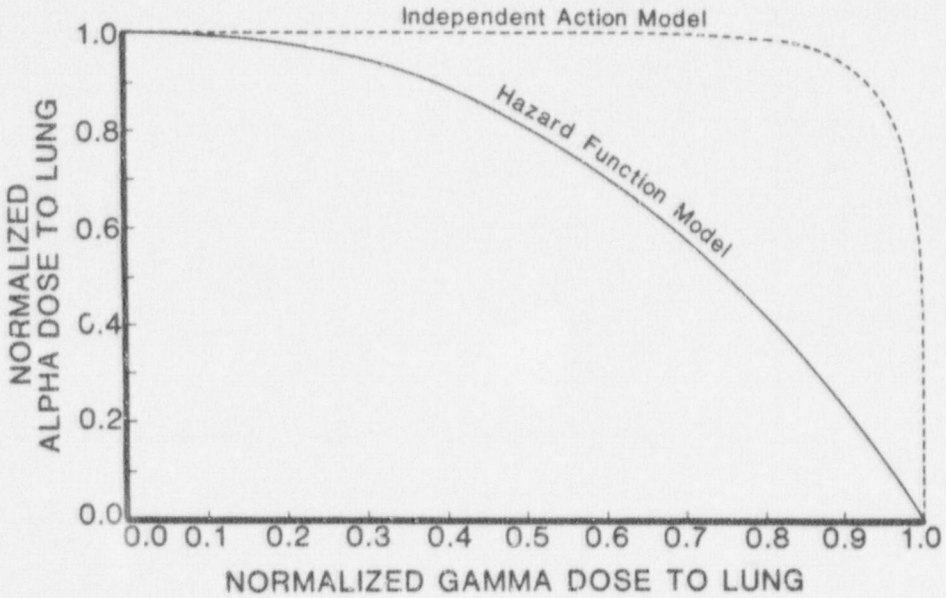

Figure 4.3 Same isobologram curves as in Figure 4.2, but plotted as a function of the normalized alpha dose XL_a (i.e., absorbed dose in Gy divided by normalization parameter 35 Gy) and normalized gamma dose XL_g (i.e., total gamma dose in Gy to lung divided by normalization parameter 10 Gy).

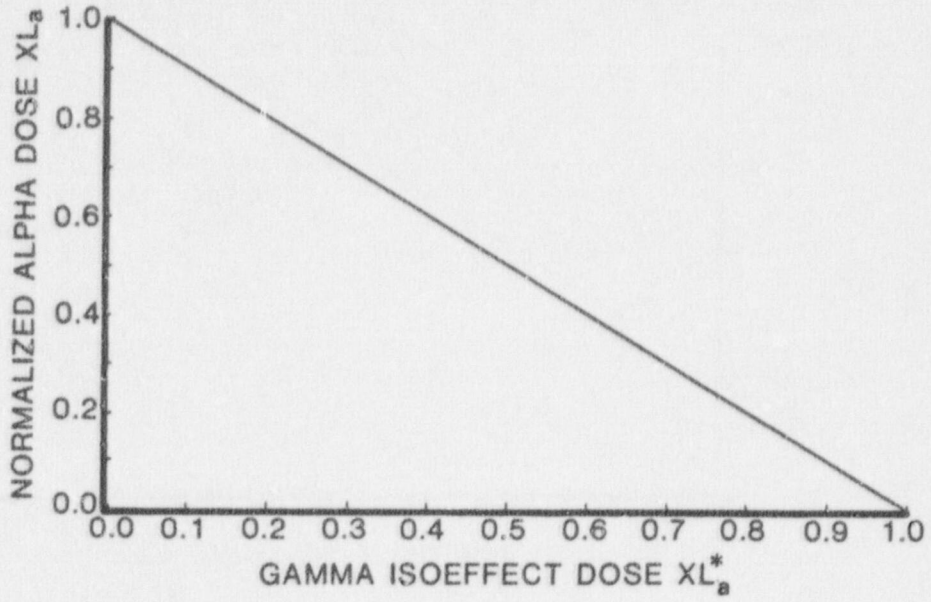

Figure 4.4 Same isobologram curve as in Figure 4.2 (curve based on the hazard-function model), but plotted in terms of the normalized alpha dose XL_a and isoeffect dose XL_a^* (also a normalized dose which accounts for the effects of the external gammas). The linear relationship implies that XL_a and XL_a^* are additive.

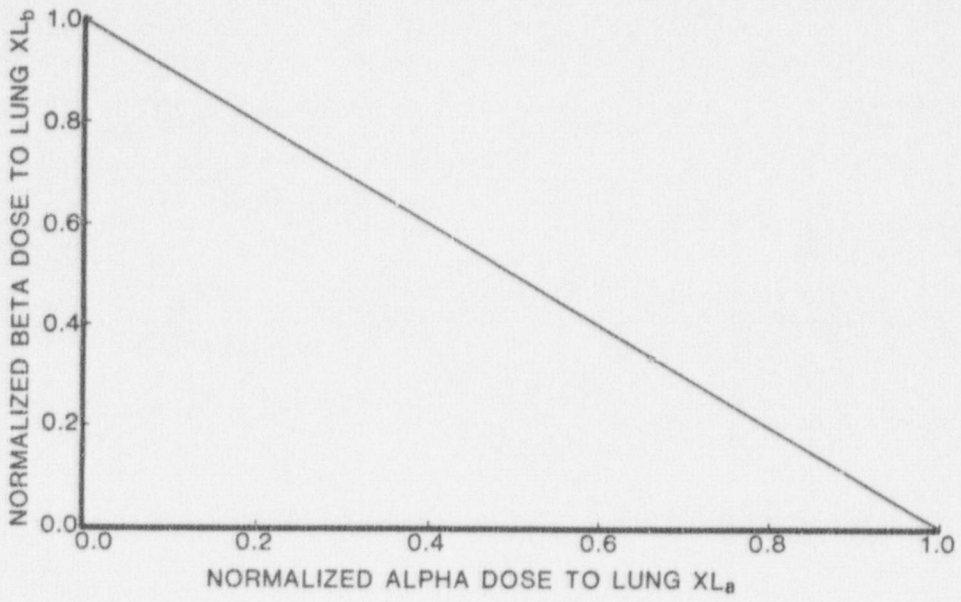

Figure 4.5 Isobologram at the 50% level for death from RPPF after chronic alpha plus chronic beta irradiation of the lung. Results based on studies in rats (Scott et al., 1988b).

4.11 COMPETING RISKS

The hazard-function modeling approach provides an easy way to treat competing risks of lethality. For example, if HL, HL, and HGI represent lethality hazards due to injury to the lung, bone marrow, and gastrointestinal tract, respectively, then the overall lethality hazard for death from early effects can be estimated using

$$H_{early} = HB + HL + HGI. \tag{4.14}$$

We can use Eq. 4.14 to predict the D_{50} for death from RPPF for the study in this project in which dogs were exposed (total-body) to 235 rad external gamma radiation followed by inhalation exposure to $^{239}PuO_2$ (Filipy et al., 1988). We assume that exposure to the external gamma radiation accelerated the occurrence of death from RPPF, so that most of the deaths from RPPF that would have occurred, did so within the 1-year observation period. In this case, the observed alpha D_{50} for 1-year lethality can be used as an estimate of the D_{50} for death from RPPF. For a 235 rad external gamma dose to the bone marrow (uniformly distributed), a shape parameter of 10 (Scott et al., 1988a), and a D_{50} of 243 rad (Filipy et al., 1988), HB will be equal to $\ln(2)*(235/243)^{10}$, or 0.5. Since 235 rad to the gastrointestinal tract (small and large intestines) would be far below the threshold dose for lethal injury (Scott and Hahn, 1989), HGI can be neglected in this example. Also, an external gamma dose of 235 rad to the lung would be far below the threshold for lethal injury, so that the external dose to the lung can be neglected. Thus, by substitution into Eq. 4.14, based on these results along with the expression from Eq. 4.1 for lethality hazard, one can arrive at the following competing risk relationship for dogs receiving 235 rad external gammas + a dose D (in 1-year rads) from internal alpha irradiation of the lung:

$$H_{early} = 0.5 + 0.693(D/3500)^5. \qquad (4.15)$$

The lethality hazard of 0.5 from injury to the bone marrow corresponds to a risk of 1-exp(-0.5) which equals 0.39 or about a 40% risk. An alpha dose D (1-year rad) to the lung leads to a lethality hazard of $0.693(D/3500)^5$, where the 5 represents the shape parameter for chronic internal irradiation of the lung, and the 3500 (in 1-year rad) is the normalization parameter for alpha irradiation. The 3500 rad estimate is based on data for dogs exposed by inhalation to ^{239}Pu and followed for 3 years (Scott et al., 1986). Note that the quotient (D/3500) represents the normalized alpha dose to lung.

Eq. 4.15 can be used to calculate the expected D_{50} (for the competing-risk model) for internal alphas when the external gamma dose to the total body is 235 rad. This is done by simply setting H_{early} equal to ln(2), or 0.693, and solving for D, which in this case gives the D_{50} estimate. One then obtains the estimate D_{50} = 2700 rad (27 Gy), which represents a 1800 rad (18 Gy) reduction. A 2500 rad (25 Gy) reduction was reported (Filipy et al., 1988).

It is important to note that the 2700 rad value was predicted without having to assume a synergistic interaction between injury to the bone marrow and to the lung. However, the results of the PNL alpha-plus-gamma study in rats clearly demonstrated that total-body exposure to external gammas can shift the survival-time distribution for death caused by chronic alpha irradiation to much earlier times.

CHAPTER 5
DISCUSSION

The fixed-parameter, hazard-function models for radiation-induced lethality from RPPF and for respiratory functional morbidity that were presented can be used in nuclear accident risk assessment. Calculations are based on the normalized dose X, rather than on the cumulative absorbed dose D, to facilitate accounting for dose rate and LET effects.

The normalized dose X functions in a similar way for nonlinear nonstochastic effects as does the dose equivalent (in rem or Sv) for linear-nonthreshold stochastic effects. It provides an equivalent effects dose scale for effects such as death from RPPF or from hematopoietic injury.

In the ideal case, the normalized dose for lethality from RPPF or respiratory functional morbidity would be determined by evaluating an integral that allows one to account for effects of a continuously changing instantaneous dose rate. For most nuclear accident scenarios of interest, the integral would have to be evaluated numerically, so that a nearly exact solution would require a large amount of computer time. However, an approximation to the integral can be achieved by using the fixed-parameter model presented.

The fixed-parameter hazard-function model was shown to adequately predict the D_{50}'s for death from RPPF after inhalation exposure of rats to mixtures of the high energy beta emitters ^{90}Y + ^{90}Sr or to the low energy beta emitter ^{147}Pm when inhaled in an insoluble form.

Use of the hazard-function model also allowed estimation of the D_{50} for death from RPPF for brief external thoracic gamma irradiation of the lung of F344 rats, based on data for combined exposure to external (total-body) gammas + internal alphas, and on data for exposure to internal alphas only. The estimate for the D_{50} obtained for external gammas was 1400 rad (14 Gy) to the lung, which was quite similar to values of 1500 rad (15 Gy) and 1700 rad (17 Gy) derived from thoracic exposure data (Cardozo et al., 1985; Kurohara and Casarett, 1972).

The results of the combined external gamma + internal alpha studies indicate that the reduction in the D_{50} for internal alpha irradiation due to total-body exposure to external gammas can be adequately explained by the high, dose-rate exposure of the lung to external gammas without having to assume a synergistic interaction between injury to the bone marrow (or other organs) and the lung. The results also indicate that, assuming that the interaction effects between lung and bone marrow are negligible, the competing-risk model (Scott and Hahn, 1985, 1989) may be adequate for nuclear accident risk assessment.

The hypothesis that the interorgan-interaction term is negligible is also supported by data for dogs that inhaled beta-emitting radionuclides in soluble forms so that significant doses were delivered to both the lung and bone marrow (McClellan et al., 1982). The data did not indicate a sensitization of the lung due to irradiation of the bone marrow.

The results presented indicate that chronic low- or high-LET doses required for respiratory functional morbidity are about a factor of 2 less than those required for lethality. The results also indicate that the same model used for lethality from RPPF can also be used for morbidity from injury to the lung if the normalization parameters for lethality are divided by a factor of 2.

The results presented in this report summarize the theoretical and experimental research on early and continuing effects of irradiation of the lung carried out intermittently at the ITRI and at PNL over about an 11 year period. It is our view that the morbidity and lethality hazard-function models presented should be adequate for nuclear accident risk assessment. However, if used out of the context of nuclear accident consequence modeling, they may function in a less-than-satisfactory manner.

The model parameters for brief exposure to external gamma radiation are based on data for man. The model parameters for chronic alpha and chronic beta irradiation are based on animal

data; however, there is no evidence that suggests that they would be very different for man. Because model parameters based on dogs adequately predicted lethality from RPPF in rats after chronic beta irradiation, we feel more confident that the lethality model will also be adequate for predicting lethality in man. However, the model may underestimate the effectiveness of the alpha irradiation, because the D_{50} used for alphas is based on 3-year follow-up and there is evidence that the risk of death from RPPF may persist for as long as 7 years during chronic alpha irradiation (Muggenburg et al., 1988). For this reason, risk assessors may want to reduce the D_{50} of 3500 rad used for alpha irradiation of the lung by some adjustment factor. An alpha RBE of 10 relative to ^{90}Sr betas, when based on total absorbed dose, would suggest reducing the D_{50} from 3500 rad to 3000 rad. With an RBE of 20, it would be reduced to 1500 rad.

While uncertainty evaluation is important for any risk assessment, a discussion of uncertainties related to predicting lethality and morbidity cases after a nuclear accident is beyond the scope of this report. However, uncertainties will be discussed in detail in a separate follow-on report to NUREG/CR-4214 SAND85-7185 (1985).

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APPENDIX A

ANALYTICAL SOLUTION FOR NORMALIZED DOSE

From Eq. 4.10, XL_b is given by

$$XL_b = \int \dot{D}^* \theta(\dot{D})^{-1} dt, \tag{A.1}$$

where the normalization function $\theta(\dot{D})$ has replaced $D_{50}(\dot{D})$ in Eq. 4.10 of the text. The expression $\dot{D}^* \theta(\dot{D})^{-1} dt$ represents the increment dX in the normalized dose X that occurs in the infinitesimal exposure time interval (t, t+dt).

An analytical solution to Eq. A.1 can be found for the case where the internal beta plus gamma dose rate to the lung (or any critical organ of interest) decreases according to the dose rate pattern:

$$\text{Dose rate} = A\exp[-B^*t], \tag{A.2}$$

where A is the initial dose rate, B is a fixed parameter, and t is the exposure time. To calculate the normalized dose X, one has to specify the form of the normalization function $\theta(\dot{D})$ that predicts the D_{50} as a function of the instantaneous dose rate. For acute lethality from irradiation of the bone marrow, a normalization function that was found to adequately represent available D_{50} data for mammals, including man, was given by (Scott et al., 1988a; Scott and Hahn, 1980)

$$\theta(\dot{D}) = \theta_1 \dot{D}^{-1} + \theta_\infty, \tag{A.3}$$

where θ_∞ is positive and gives the asymptotic value of the D_{50} expected to occur after exposure at a very high dose rate (i.e., after a prompt exposure) that overwhelms the recovery (repopulation of cells) and repair mechanisms during irradiation. The parameter θ_1 is positive and the quotient $\theta_1/\dot{D}$ gives the increase in the D_{50} that occurs during protracted exposure at the fixed dose rate $\dot{D}$ due to repair and recovery. Equation A.3 was also assumed to be applicable to the lung for death from RPPF, but with a different set of parameters than for lethality from the hematopoietic mode (Scott and Hahn, 1989).

Substitution of the expression for $\theta(\dot{D})$ in Eq. A.3 into Eq. A.1, along with the expression for the instantaneous dose rate from Eq. A.2 produces the solution $XL_b(t)$, as evaluated at exposure time t, given by

$$XL_b(t) = DOSE(t)/\theta_\infty - \theta_1 Z(t)/B\theta_\infty^2, \tag{A.4}$$

where

$$Z(t) = \ln\{(A\theta_\infty + \theta_1)/(A\theta_\infty \exp[-Bt] + \theta_1)\}. \tag{A.5}$$

The negative sign in Eq. A.4 arises because protraction of the exposure reduces the dose X. Note that Eq. A.4 can be used to define an exposure time-dependent, dose-rate protraction factor (DRPF) for the exponentially decaying pattern of irradiation considered (Eq. A.2). When expressed in terms of the equivalent prompt dose (EPD), the dose-rate protraction factor is given by

$$DRPF = DOSE(t)/EPD(t), \quad (A.6)$$

where the EPD is given by

$$EPD(t) = XL_b(t)*\theta_\infty.$$

The star indicates multiplication. In the limit as t goes to infinity, Eq. A.4 reduces to the normalized dose (as a function of the potential infinite dose, PID) given by

$$XL_b = PID/\theta_\infty + \theta_1 \ln\{\theta_1/(A\theta_\infty + \theta_1)\}/B\theta_\infty^2. \quad (A.7)$$

Both the DOSE(t) in Eq. A.4 and the PID in Eq. A.7 represent cumulative absorbed radiation doses in rad or a similar unit (e.g., Gy). The PID is the potential dose that could accumulate if irradiation continued long enough so that the remaining activity in the organ of interest contributes essentially no additional radiation dose.

Eq. A.7 was used, along with data for death from RPPF after chronic beta irradiation of the lung of dogs (McClellan et al., 1982), to estimate the parameter θ_1. The parameter θ_∞ was fixed at 1000 rad (10 Gy), assuming the lung of dogs to be of similar sensitivity to the lung of man; XL_b was set to 1 (i.e., a median lethal dose), and the PID for 50% lethality previously estimated from the data (Scott and Seiler, 1984), along with the initial dose rate to the lung that corresponded to that PID were entered into the right-hand side of Eq. A.7, with only θ_1 being unknown; θ_1 was then found as the value that made the right-hand side of Eq. A.7 equal to 1. The results obtained are given in Table A.1 along with an estimate we obtained from data for rats that received thoracic exposure to X rays at a fixed high or low dose rate (Cardozo et al., 1985).

Results of a sensitivity analysis indicate that small-to-moderate changes in the value assigned to θ_∞ did not alter the estimates obtained for θ_1; that this would be the case can be seen from Eq. A.3. For chronic, low-dose-rate irradiation, $\theta_1/\dot{D}$ will be quite large compared to θ_∞, so that estimates of θ_1 from data obtained at very low dose rates will depend only weakly on the value of used for θ_∞. The 5170 rad^2/min used for man in Eq. 4.11 of the text is based on the results in Table A.1. The 1000 rad value used in Eq. 4.11 of the text represents the value used for θ_∞, and is based on data for man (Scott and Hahn, 1988).

Table A.1
Estimates of Dose-Rate Model Parameter θ_1 for
Pulmonary Syndrome Mode of Lethality

Species	Radiation Type	Parameter Estimate[a] (Gy^2/hr)	Reference
Dog	^{90}Y Beta	46	McClellan et al., 1982
Dog	^{91}Y Beta	21	McClellan et al., 1982
Dog	^{144}Ce Beta	38	McClellan et al., 1982
Dog	^{90}Sr Beta	21	McClellan et al., 1982
Rat	X Rays	28	Cardozo et al., 1985
		Average 31 ± 9.8 Gy^2/hr	

[a]Lower and upper bounds can be taken as 10 and 50 Gy^2/hr based on these data. To convert to rad^2/min, multiply values by 166.7.

APPENDIX B
SHAPE PARAMETER FOR SIMULTANEOUS EXPOSURES

This section deals with estimation of the shape parameter V, for death from RPPF, for simultaneous exposure of the lung to different ionizing radiations. It is assumed, based on information provided in the text, that the shape parameter derived for death from RPPF is also applicable to respiratory functional morbidity.

Computer simulations related to death from RPPF after combined exposure to different radiations have been previously carried out using the hazard-function approach, whereby increments in the cumulative hazard were calculated numerically based on isoeffect absorbed doses (Scott et al., 1986). In the simulations carried out, fractional contributions to the total dose by each radiation did not vary with total dose, but were fixed.

Results of analysis of the simulated data indicated that when both the D_{50} and the shape parameter V differ for two types of radiations, the shape parameter for simultaneous exposure to both types depends, in a complicated way, on the fractions of the total absorbed dose due to each type (Scott et al., 1986). A subsequent analysis of the simulated data indicated that when the normalized dose is used, the shape parameter for the simultaneous exposure can be adequately predicted by the reciprocal relationship

$$1/V_{12} = g_1/V_1 + g_2/V_2, \qquad (B.1)$$

where g_1 and g_2 are radiation-specific fractions of the normalized dose, V_1 is the shape parameter for radiation type 1, V_2 is the shape parameter for radiation type 2, and V_{12} is the shape parameter for simultaneous exposure to both.

In the special case where the D_{50}'s for the two types of radiations are the same, but the shape parameters differ, g_1 and g_2 in Eq. B.1 can be replaced by respective fractions of the absorbed dose to the lung, given by f_1 and f_2.

Using the subscript g to indicate gamma irradiation and the subscript a to indicate alpha irradiation, one arrives at the following relationship for simultaneous gamma and alpha irradiation of the lung:

$$1/V_{ga} = g_g/V_g + g_a/V_a. \qquad (B.2)$$

For death from RPPF, V_g and V_a were estimated from animal data to be 12 and 5, respectively.

For gamma and for beta irradiation of the lung, the D_{50}'s have been assumed to be the same, while available data has indicated different shape parameters. Using the subscript b to indicate beta irradiation, one arrives at the following relationship for simultaneous gamma and beta irradiation of the lung:

$$1/V_{gb} = f_g/V_g + f_b/V_b, \qquad (B.3)$$

where V_b is estimated to be 5 (see text).

For simultaneous alpha, beta, and gamma irradiation of the lung, the following empirical relationship is recommended for estimating the shape parameter:

$$1/V = g_{gb}/V_{gb} + g_a/V_a, \qquad (B.4)$$

where

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Results of analysis of the simulated data indicated that when both the D_{50} and the shape parameter V differ for two types of radiations, the shape parameter for simultaneous exposure to both types depends, in a complicated way, on the fractions of the total absorbed dose due to each type (Scott et al., 1986). A subsequent analysis of the simulated data indicated that when the normalized dose is used, the shape parameter for the simultaneous exposure can be adequately predicted by the reciprocal relationship

$$1/V_{12} = g_1/V_1 + g_2/V_2, \qquad (B.1)$$

where g_1 and g_2 are radiation-specific fractions of the normalized dose, V_1 is the shape parameter for radiation type 1, V_2 is the shape parameter for radiation type 2, and V_{12} is the shape parameter for simultaneous exposure to both.

In the special case where the D_{50}'s for the two types of radiations are the same, but the shape parameters differ, g_1 and g_2 in Eq. B.1 can be replaced by respective fractions of the absorbed dose to the lung, given by f_1 and f_2.

Using the subscript g to indicate gamma irradiation and the subscript a to indicate alpha irradiation, one arrives at the following relationship for simultaneous gamma and alpha irradiation of the lung:

$$1/V_{ga} = g_g/V_g + g_a/V_a. \qquad (B.2)$$

For death from RPPF, V_g and V_a were estimated from animal data to be 12 and 5, respectively.

For gamma and for beta irradiation of the lung, the D_{50}'s have been assumed to be the same, while available data has indicated different shape parameters. Using the subscript b to indicate beta irradiation, one arrives at the following relationship for simultaneous gamma and beta irradiation of the lung:

$$1/V_{gb} = f_g/V_g + f_b/V_b, \qquad (B.3)$$

where V_b is estimated to be 5 (see text).

For simultaneous alpha, beta, and gamma irradiation of the lung, the following empirical relationship is recommended for estimating the shape parameter:

$$1/V = g_{gb}/V_{gb} + g_a/V_a. \qquad (B.4)$$

where

$$g_{gb} = g_g + g_b \tag{B.5}$$

and

$$g_a + g_b + g_g = 1. \tag{B.6}$$

Note that when the alpha dose is set to zero (i.e., $g_a = 0$), Eq. B.4 gives $V = V_{gb}$, as expected. When the alpha and beta doses are both set to zero (i.e., $g_a = 0$, $g_b = 0$), $V = V_g$, as expected. When only the gamma dose is set to zero, $V = V_a$, since $V_a = V_b$ (see text). One should see from these examples that Eq. B.4 yields the appropriate marginal values, and therefore represents a plausible (but unproven) predictive model.

Eqs. B.1 through B.4 imply that the shape parameter will change as the total absorbed dose changes when g_a, g_b, and g_g change with dose. Because the cumulative hazard is estimated using

$$H = \ln(2)X^V, \tag{B.7}$$

and because V, which is fixed in the classical model, can change with dose, a departure from the classical Weibull model should arise for many complex mixtures. This, however, poses no problem for combined chronic alpha and beta irradiation of the lung because the shape parameter for death from RPPF is the same for both types of radiation. For brief exposure to external gammas, followed by chronic, internal alpha plus beta irradiation, Eq. B.4 is not applicable. As indicated in the text, a shape parameter of 5 can be used for this latter case, provided an isoeffect (normalized) dose is calculated to account for the effects of the brief gamma irradiation.

APPENDIX C

LIST OF PUBLISHED MANUSCRIPTS

Scott, B. R., and Hahn, F. F. (1989): Early and Continuing Effects. In Health Effects Model for Nuclear Power Plant Accident Consequence Analysis, Volume II, Chapter I, NUREG/CR-4214, Final Version.

Scott, B. R. (1988): A Radiation Protection Approach to Assessing Population Risks for Threshold Type Radiobiological Effects. In Proceedings of the 25th Hanford Life Sciences Symposium on: Radiation Protection - A Look to the Future. Health Phys. 55: 463-470.

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13. ABSTRACT (200 words or less)

This report provides a hazard-function model for estimating the risk of death from radiation pneumonitis and/or pulmonary fibrosis following a light-water nuclear power plant accident. A similar model is also provided for estimating the prevalence of respiratory functional morbidity among those that survive death from acute effects. Hazard-function models for lethality and for morbidity were constructed using the cumulative hazard estimator H, which is related to the risk estimator R through the equation $R = 1-\exp(-H)$. The estimator H can be calculated using information provided in the report. The method of calculation depends on the exposure scenario. In general, the total normalized dose X for lethality or for morbidity is calculated. For lethality, $X = 1$ corresponds to a median lethal dose (LD_{50}); for morbidity, $X = 1$ corresponds to a median effective dose (ED_{50}). H is related to X by the equation $H = \ln(2)X^{V}$, where V depends on the type of radiation (or radiations) involved. Contributions to X can arise from each of two main modes of exposure: (1) Brief exposure of the lung, at a relatively high dose rate, to mainly external gammas, followed by (2) chronic internal alpha, and/or beta, and/or gamma irradiation of the lung. Equations are provided for calculating the contributions to X from both modes of exposure. While uncertainty evaluation is important for any risk assessment, an evaluation of the uncertainties related to predicting lethality and morbidity cases after a nuclear accident is beyond the scope of this report. However, uncertainties are discussed in detail in a separate, follow-on report (NUREG/CR-4214) to be published in 1989.

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