AUGUST 1984

HANDBOOK FOR ESTIMATING HEALTH EFFECTS FROM EXPOSURE TO IONIZING RADIATION

compiled by Rosalie Bertell, Ph.D., G.N.S.H.

Institute of Concern for Public Health
Toronto, Ont., Canada

Ministry of Concern for Public Health
Buffalo, N.Y., USA

International Radiation Research
and Training Institute
Birmingham, England, U.K.

HANDBOOK FOR ESTIMATING HEALTH EFFECTS FROM EXPOSURE TO IONIZING RADIATION

compiled by Rosalie Bertell, Ph.D., G.N.S.H.

Published and distributed by:

Institute of Concern for Public Health
67 Mowat Avenue, Suite 343
Toronto, Ontario M6K 3E3, **Canada**

Ministry of Concern for Public Health
5495 Main Street, Suite 147
Buffalo, New York 14221, **USA**

International Radiation Research and Training Institute
Regional Cancer Registry, Queen Elizabeth Medical Centre
Birmingham, England B15 2TH, **UK**

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF TABLES (Continued)

INTRODUCTION

Part of this Handbook was developed as a joint project with the Institut für Energie und Umweltforschung (IFEU), Heidelberg, F.R.G., in response to a request from the West German Parliament. The F.R.G. was in the process of building its first breeder nuclear reactor, Kalkar, near the border with the Netherlands and the probable consequences of a serious reactor accident were being debated in both countries. To resolve the debate the West German Parliament contracted with both the scientists in Karlsruhe, nuclear proponents, and the scientists in Heidelberg, nuclear critics, to estimate the severity of nine accident scenarios for the 300 MWe Kalkar breeder reactor relative to comparable accidents at a 1000 MWe conventional nuclear reactor. The question asked was: Is this small breeder reactor at least as safe as the largest conventional nuclear reactor now licensed in the F.R.G.? The task included offering health effect estimates and, if these differed from those commonly accepted in nuclear circles, to explain the difference.

IFEU undertook to calculate the nuclear plant inventory of radioactive particles and the probable emissions into air, water and land for each accident scenario. They then traced the pathways through which the people living in the vicinity of the plant might be exposed to the radioactive material. This information was used to calculate average radiation doses to the population.

This Handbook was then used to convert doses to estimates of the number of severe health effects, including early deaths from non-malignant damage to tissue, cancers, genetic and teratagenic damage, which might result from each accident. The complete report of the relative hazard of the breeder reactor accident prepared by IFEU is now available only in German.

There are many other situations in which it is helpful to have a guide for "translating" human radiation exposure doses into probable health effects, for example: a labor union faced with evaluating a list of worker radiation exposures, a physician deciding on the risks and benefits of various X-ray procedures, or a citizen organization trying to deal rationally with a nuclear power plant accident. In view of these needs, the Handbook has been expanded and adapted for these uses. The English language version has been partially funded by the International Radiation Research and Training Institute.

It is presumed that the reader using the Handbook has information on radiation dose to the whole body or to relevant human tissue, such as lung or bone marrow. Such dose information is provided at least in an approximate form by radiation film badges or by tables of average X-ray dose from various medical procedures. It is beyond the scope of the Handbook to provide specific dose information. Appendices B and C give some approximate dose information on medical procedures.

It is also important for the reader to know the source of the radiation, as alpha particles (high linear energy transfer — LET) do different biological damage than X-ray (low LET).

Some radioactive materials emit rays which can penetrate the body even though the material remains outside. The most common are gamma and X-ray emitters. Some beta particles are able to penetrate the outer skin layer and do some internal damage to humans. When the radioactive particles are taken within the body through inhalation or ingestion, they can do more severe local biological damage to the cells immediately surrounding the bone, organ or tissue in which they lodge. The transport of the radioactive material within the body, and the gland, organ or tissue in which it tends to concentrate varies with the physical size, solubility and the chemical nature of the material. For example, particles must be of respirable size in order to be breathed into the lung; radioactive iodine will tend to concentrate in the thyroid gland; cesium 137 will concentrate in muscle; and strontium 90 will concentrate in bone. Damage can range from aplastic anemia or abnormal immune system reactions to a fatal cancer.

When the source of radioactivity is external to the body, the dose in rem (Roentgen Equivalent Man) and the dose in rad (Radiation Absorbed Dose) are the same. Sometimes the terms are used in interchangeably in this Handbook. When estimates are taken from another source they are normally quoted as given in that source. There is one caution needed here, especially when using the Handbook for medical applications. Diagnostic medical X-rays are at the "soft", less penetrating end of the ionizing radiation spectrum. The reason X-ray is appropriately used for imaging bone is that it passes through soft tissue more readily than through bone. A diagnostic chest X-ray for example, delivers about a 0.045 rad dose to the chest. This "translates" to a 0.045 rem skin dose, a 0.029 rem whole body dose, and a 0.004 rem dose to bone marrow. In contrast, a 0.045 rad or rem gamma dose (site unspecified) would, because of the greater penetrability of gamma rays, usually mean a 0.045 rem dose to the whole body and a 0.045 rem dose to bone marrow.

When the source of radiation is internal to the body, or when dose to a particular organ is considered, the rad dose to that organ from low LET radiation is used in the Handbook. At times, especially with reference to plutonium contamination, the high LET rad dose is also given. The reader unfamiliar with this terminology will need to consult a basic radiation protection textbook. As a "rule of thumb" for most practical purposes, rad and rem doses to organs are equivalent for X-ray and gamma sources. Internal rad doses from beta particles, fast neutrons, or protons are multiplied by 10 to get the rem dose; and internal rad doses from alpha particles are multiplied by 20 to get the rem dose.

The Handbook provides information on estimates of health effects given in publications by the United Nations, the U.K. National Radiation Protection Board, the U.S. National Academy of Science, and various other scientific sources for comparative purposes. A selection of credible upper and lower risk estimates is then made as a "best estimate" at this time in history. Since radiation health questions are being intensely researched at this time, it is expected that the Handbook will be periodically revised. This direct method of presentation and format should facilitate such an update when needed in response to new information. Also, since any selection of estimates may be subject to criticism, the reasons for the author's selection are given. The user of the Handbook may choose different estimates as might be appropriate because of a differing set of circumstances or greater need of erring on the side of caution.

No attempt is made to estimate what level of risk is "acceptable" to the public relative to some benefit gained. This is a political not a scientific question. No attempt is made to evaluate present radiation protection guidelines, but the interested reader can calculate the cost in lives under present "permissible" exposure levels for workers and the general public by using appropriate tables.

For readers using the new International System of radiation units,

1 rad = 0.01 Gray
1 rem = 0.01 Sievert

To estimate the number of cancers induced by an average 1 Gray exposure to a population of one million people, multiply the estimate for a 1 rad dose by 100.

I am grateful to Norine Pigeau and Kathy Brouwer who patiently typed and retyped tables, to Dr. Alice Stewart and Bernd Franke who reviewed the manuscript, and to all of the staff in Toronto and Heidelberg who encouraged the undertaking and proof read the papers. I hope that readers will feel free to build upon this basic Handbook, converting it to a hundred and one practical uses. If you send us helpful suggestions or additions we will be glad to consider them for the next edition.

Rosalie Bertell, Ph.D., G.N.S.H.
67 Mowat Avenue, Suite 343
Toronto, Ontario
M6K 3E3, Canada

SECTION I

DEATHS DUE TO ACUTE EXPOSURE TO IONIZING RADIATION

DEATHS DUE TO ACUTE EXPOSURE TO IONIZING RADIATION

Situations of exposure to ionizing radiation causing death within a relatively short period of time to a healthy "average" adult may be classified as follows:

1. Exposure to the whole body or to a significant portion of bone marrow,
2. Exposure of the tracheo-bronchial pathway and lungs, and
3. Exposure of the gastro-intestinal tract.

The biological mechanisms involved include massive cell killing and cell sterilization which disrupts the normal functioning of tissues and organs, or the destruction of cell membranes which results in leakage of fluids and electrolytes. Recovery from a radiological trauma is dependent on the victim's general health, age, medical history, nutrition and medications, and access to medical care. It also depends on the type of radiation and the proportion of tissue destroyed. Therefore these estimates are highly variable with given populations and medical delivery systems.

It is expected that the death process for persons in critical condition at the time of a radiological emergency would be accelerated and the ability of some to recover health would be negatively affected. These persons, who will die because of the radiation exposure, usually are not counted among the radiation fatalities because the actual cause of death is the underlying frailty rather than massive tissue damage by the radiation. A similar situation occurs with sudden changes in temperature or air pressure.

Since the general public will not make a distinction between "radiation caused" and "radiation assisted" deaths, their perception of the "cost" of a severe reactor accident may differ from the perception of the experts.

Section 1: Whole Body and Bone Marrow Dose

Estimates of radiation induced early deaths depend on three basic parameters: the length of time over which the dose is calculated, the threshold for radiation induced deaths, and the dose at which half of the population would be expected to die (LD_{50}). Table 1 gives the parameters used in major nuclear reactor accident studies, and those used in the present analysis.

Table 1

EARLY DEATHS FROM WHOLE BODY OR BONE MARROW EXPOSURE

Study	Dose Integrated over	Threshold in Rad or Rem	LD_{50} in Rad or Rem
RSS - 1975 (1)	60 days	330	540
NRPB - 1976 (2)	60 days	300	650
CRBRP - 1977 (3)	30 days	150	350
RHP - 1977 (4)	1 year	Lower: 200	400
		Upper: 330	540
Fetus (5)	—	10	80
Handbook: Adult	1 year	Lower: 150	350
		Upper: 330	540
Parental/Fetus	2 years	10	80

In the RSS — 1975 (1) report, and those based on its findings, the acute dose of radiation was defined to be that received over the first seven days after the accident plus one-half the dose from day 8 to day 60. This was based on the hypothesis that the dose from fission releases in a light water reactor accident decrease with time and a second hypothesis that protracted doses are only half as effective (for cell killing) as acute doses. The RSS — 1975 (1) report also omits consideration of radionuclides with half lives less than 30 minutes because of an assumed slow dispersion of radioactive chemicals after an accident in a light water reactor.

These assumptions do not hold for a breeder reactor accident. This Handbook agrees with the RHP — 1977 (4) study that radiation dose should be integrated for one year after a breeder reactor accident. The bone marrow dose from inhaled soluble actinides increases by a factor of 20 between day 30 and one year after an accident. The actinide release from a breeder reactor accident is of much greater significance than actinide release from a light water reactor accident.

Since there is evidence that protracted alpha radiation doses can actually increase cell killing and cell sterilization by preventing the slower, less error-prone cell repair process from operating (6), no reduced effect because of protracted dose is assumed. The acute mortalities may be increased; hence the Handbook estimates are "best estimates", not upper bounds of lethality.

A breeder reactor accident may be highly energetic, making dispersal of short-lived radioactive chemicals important. It is also likely that damage to lungs and/or gastro-intestinal tract would interact with bone marrow damage, reducing the individual's ability to survive the bone marrow damage increase after the 30 day period. No assumption of increased lethality due to this synergism has been incorporated into mortality estimates. This makes the estimates conservative and perhaps too low.

The threshold and LD_{50} doses in rems are the lower and upper "best estimates" currently proposed in the literature. There is some question about the legitimacy of using a threshold dose of 150 rem, since there were no early deaths among the people of Rongelap, in the Marshall Islands, who were exposed to an average dose of 175 rem from weapon testing. The Rongelap population was small, about 64 people, and evacuation took place 48 to 72 hours after the initial exposure. After evacuation the people received medical support and had access to unpolluted water, food and air, These conditions could not be duplicated with a population of several million after a severe reactor accident. It might also be noted that the Marshallese experienced severe health effects, including beta burns, vomiting, diarrhea, epilation (falling out of hair), and hemopoietic depression (7). The youngest exposed person was one year old. He survived the acute effects but died of leukemia as a teenager. There was an increase in still births and miscarriages for five years following the accident (8). It seems rash to assume that an exposure of this severity would not have caused fatalities under non-evacuation conditions.

Because of the significance of pre-conception exposure of the sperm and ovum (9, 10), for subsequent embryonic, fetal, neonatal and infant deaths (to 1 year of age), the significant dose is integrated over two years. The dose is to the parents prior to conception and to the embryo or fetus in utero. The estimate of threshold at 10 rem is non-conservative since a 13% death rate has been reported from medical diagnostic X-ray in the 1 rem range to parents and/or fetus (11). Because of the difference in quality between alpha and X-rays, the alpha rays having a higher probability of destroying the sperm or ovum prior to conception, the threshold proposed by Brent and Garson was used. Alpha ray destruction of sperm and ovum in early stages of development would tend to decrease estimates of post-conception fatalities.

For the doses above 600 rem both males and females are rendered sterile (9, 10). Loss of a portion of the ovum in the female, at any dose, is permanent. Loss of stem cells in the male testes (doses below 600 rem) causes temporary infertility or sterility. It may take years to repopulate these stem cells and restore fertility (12).

The data on the Marshallese indicated that for the five years after the exposure accident 21.1% of the pregnancies where both parents were exposed terminated in abortions, miscarriages and neonatal deaths, as opposed to 12.8% for the unexposed controls. Where the mother only was exposed, 54.5% of the pregnancies were terminated in loss, and where the father only was exposed 25.0% were terminated in loss (8). This would seem to indicate a higher rate of early embryonic loss, not easily detectable, for the most seriously deficient embryos in the cases where both parents were exposed.

It is to be remembered that persons surviving severe radiation damage may experience permanent chronic disability because of the tissue's inability to recover fully. Likewise, the unborn who survive in utero damage may be permanently retarded mentally and/or physically as a result of their exposure.

REFERENCES FOR SECTION 1: Whole Body and Bone Marrow Dose

1. RSS: U.S. Nuclear Regulatory Commission, "Reactor Safety Safety — An Assessment of Accident Risks in U.S. Commercial Power Plants." NUREG 75/014 (WASH 1400) 1975.
2. NRPB: The National Radiological Protection Board, Harwell, U.K. Study: "Human Exposure to Radiation following the Release of Radioactivity from a Reactor Accident: A Quantitative Assessment of the Biological Consequences" by H. Smith and J. W. Stather, November 1976.
3. CRBRP: "Clinch River Breeder Reactor Plant Safety Study — An Assessment of Accident Risk from the Clinch River Breeder Reactor Plant." March 1977 Volume 1: Main Report.
4. RHP: "Relative Hazard Potential" — The Basis for Definition of Safety Criteria for Fast Reactors", by L. Cave and D. Ilberg, February 1977.
5. Brent and Garson. "Radiation Exposure in Pregnancy". **Current Problems in Radiology**, Mosby et al. Chicago Yearbook, Medical Publishers Inc., Vol. 2 (1972).
6. BEIR III. "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980." U.S. National Academy of Science Press. pp. 235-236.
7. Conard, R. et al. "A Twenty-year Review of Medical Findings in a Marshallese Population Accidently Exposed to Radioactive Fallout." Brookhaven National Laboratory BNL #50424 (1975) pp. 10-14.
8. Conard R. et al. ibid p. 16.
9. Bross, I. and Natarajan, N. "Genetic Damage from Diagnostic Radiation." **Journal American Medical Association** 237: 2399 (1977).
10. Bross, I. and Natarajan, N. "Cumulative Genetic Damage in Children Exposed to Preconception and Intrauterine Radiation." **Investigative Radiology**: 15, January-February 1980.
11. Bertell, R. "Radiation Exposure and Human Species Survival." **Environmental Health Review** 25:2 pp. 43-52 (1981).
12. Rowley, M. J. et al. "The Effects of Graded Doses of Ionizing Radiation on the Human Testis." **Radiation Research**: 59, p. 665 (1974).

Section 2: Tracheo-Bronchial And Lung Dose

When radiation exposure is primarily to the tracheo-bronchial air pathways and the lungs, acute inflammation of the air sacs and conducting airways occurs, causing pneumonitis (1). In severe pneumonitis death occurs within days due to edema of the lungs followed by cardiovascular collapse.

The severity of the pneumonitis depends on the person's age, prior illness, the availability of medical support, proportion of the lung exposed, the type of radiation and duration of radiation. In patients surviving pneumonitis there are progressive lung changes, including reduction in elasticity of the air sacs (fibrosis) and loss of cilia from the conducting airways. These in turn cause difficulty in breathing, increased susceptibility to lung infections, changes in the pH of blood because of inefficient gas exchange, enlargement of the heart and general disability which may be severe, irreversible and even fatal.

Changes in lung tissue were observed in humans below 500 rems (low LET) (2). Depending on whether one used a quality factor of 168 (from ICRP #30) or 12,000 (from K. Z. Morgan's revision), this would be comparable to between 3 and 0.04 rads or 0.162 to .0022 μCi of $^{239}PuO_2$ lung burden.

Prolongation by fractionation of external radiation dose reduces the incidence of pneumonitis (3). It is not known whether chronic internal alpha irradiation would increase (by preventing cell recovery) or decrease incidence of pneumonitis. Neither fractionation nor prolongation of dose reduce fribrosis (4).

In estimating lung dose for acute lung effects, integration is over the first year and includes deaths from both pneumonitis and respiratory failure due to lung tissue damage and fibrosis. The significant presence in the lungs of insoluble (Class Y) plutonium dioxide with long residence time (10) means continued risk even if the individual survives pneumonitis. This differs from RSS-1975 (5), which assumes an integrated dose over 60 days for a light water reactor accident. The RSS accident would not be expected to release plutonium aerosols in the quantity released from a fast breeder accident of the same magnitude. This latter type accident requires that the dose be integrated over the first year.

The threshold dose of pneumonitis for the healthy adult is taken as 2,500 rads low LET exposure to lung tissue. An LD_{50} dose of 4,000 rads to lung tissue is assumed, with an LD_{100} of approximately 5,500 rads. This seems reasonable on the basis of human and animal exposure data. Since a 5,000 rad dose to the brain causes death within hours (11), a radiation exposure of the upper body including brain and lung might be fatal because of brain damage before lung damage was manifest.

The RSS-1975 (5) estimate of 19,000 rads as an LD_{50} is rejected as incorrectly extrapolated from animal data. The laboratory animals (dogs) were selected for good health and maintained in a specially designated environment with minimal smog or other air pollution and no smoking. This artificial setting could hardly be duplicated for a large human population. There is also evidence that baboon lung tissue is 4 times as susceptible to microscopic lesions (cancer induction) as are dogs (12). Assuming human lung tissue is more like baboon lung tissue than dog lung tissue, and that massive lesions are the sum of microscopic lesions, the LD_{50} estimate of 19,000 rads should be reduced to at least 4,750 rads. Further reduction because of a non-laboratory human environment would be reasonable.

If one uses the Bair 1962 findings (7) for dogs, reducing the plutonium dioxide amounts by a factor of 4 for dog to human tissue sensitivity, an LD_{93} of 1.8 to 13.2 μCi can be estimated. This is a reasonable estimate, since 1 Ci of ^{239}Pu on animal skin, which is epithelial as is the lung tissue, has high yield of micro-lesions with a 50% cancer yield or higher (13).

A comparable lethal dose for $^{239}PuO_2$ can be derived indirectly. Prior to ICRP #30, it was assumed that 0.016 Ci plutonium would cause a 15 rem/year alpha radiation dose to lungs, or equivalently a 0.3 rad/year dose with a Relative Biological Effectiveness (RBE) factor of 50 (risk of 5 x quality factor 10). The newer ICRP #30 recommendations set the maximum permissible lung burden at 0.0135 Ci plutonium, expecting to cause a 42 rem/year dose to lung tissue. This change implies that the risk figure and therefore the RBE has been revised upward. Since 0.0135 Ci plutonium is estimated to give a 0.25 rad dose of alpha energy to lung tissue, the implied new RBE recommendation is 168 for converting rads to rems for plutonium (although ICRP uses a new methodology to obtain these numbers.)

Applying this conversion factor to the estimated dose for pneumonitis fatality one obtains:

Table 2

ESTIMATED RADIATION DOSES INDUCING LUNG FATALITIES

	Rads low LET	Rads ^{239}Pu	Ci ^{239}Pu
Threshold	2,500	15	0.8
LD_{50}	4,000	24	1.3
LD_{100}	5,500	33	1.8

This is in good agreement with the findings of Bair and is confirming of the correction factor of four for dog to human tissue sensitivity. Lung fibrosis would, of course, occur well below this level of exposure.

Estimates for pneumonitis, fibrosis and lung tissue damage fatalities are for the "standard man", an average adult male in good health. No estimates are available for induced fatalities among persons with asthma, emphysema, or respiratory insufficiency prior to the reactor accident. The elderly and immature infants (i.e. those with birth weight under 2500 gm.) would be at higher risk from lung irradiation.

Table 3

MORTALITY PARAMETERS FOR ACUTE LUNG IRRADIATION

Study Subject	Dose Integrated over	% Mortality	Dose	Comments
RSS-draft RSS-final (5)	30 days 60 days	50 50	4,000 rem 19,000 rem	Used as upper and lower bounds in RHP (6)
Philips 1972 (3)	2 weeks (20 fractions)	50 incidence	3,050 rads low LET (external)	Death rate was dependent on frailty of patient
Wara 1973 (6)	2 weeks (20 fractions)	Threshold	2,500 rads low LET (external)	
Bair 1962 (7) (Beagle dogs)	Until death	93	7.1 to 53 μCi $^{239}PuO_2$	The alpha energy dose to lungs for the first year was 130 to 1,000 rads
Hahn 1975 (8) (Beagle dogs)	7-903 days	100	9,300-27,000 rads (^{90}Y)	Comparable human dose: 2,325-6,750 rads
	113-1011 days	100	8,300-60,000 rads (^{91}Y)	Comparable human dose: 2,075-15,000 rads
	143-410 days	100	28,000-140,000 rads (^{144}Ce)	Comparable human dose: 7,000-35,000 rads
	159-477 days	100	40,000-90,000 rads (^{90}Sr)	Comparable human dose: 10,000-22,500 rads
NRPB-1976 (9)	1 year	50	4,250 rads low LET	2,500 to 6,000 rads range
Handbook	1 year	50 Pneumonitis mortality	4,000 rads low LET 1.3 μCi $^{239}PuO_2$	2,500-5,500 range 0.8 to 1.8 μCi $^{239}PuO_2$

REFERENCES FOR SECTION 2

1. Spencer, H. **Pathology of the Lung.** Oxford, Pergamon Press 1973.
2. Jennings, F. L. and Arden.,A. "Development of Radiation Pneumonitis; Time Dose Factors." **Archives Pathology**: 74: 351 (1962).
3. Philips, T. L. and Margolis, L. "Radiation Pathology and the Clinical Response of Lung and Oesophagus." **Front. Radiat. Ther. Oncol.** 6: 254 (1972).
4. Rubin, P. and Casarett, G. W. **Clinical Radiation Pathology,** W. D. Saunders Co. Publishers, Philadephia 1968.
5. RSS: "Reactor Safety Study," Rasmussen. Appendix VI U.S. Nuclear Regulatory Commission, WASH-1400, 1975.
6. Wara, W. M. et al. "Radiation pneumonitis: A new approach to the derivation of time dose factors." **Cancer** 32: 547, 1973.
7. Bair, W. J. and Willard, D. H. "Plutonium inhalation studies: IV Mortality in dogs after inhalation of $^{239}PuO_2$". **Radiation Research** 16: 811, 1962.
8. Hahn. F. F. "Estimates of mortality due to radiation pneumonitis and pulmonary fibrosis after exposure to radionuclides released in a hypothetical light water reactor accident." In: **Inhalation Toxicology Research Institute Report** LF-50.Albuquerque, Lovelace Foundation.
9. "Human Exposure to Radiation following the Release of Radiactivity from a Reactor Accident: A Quantitative Assessment of the Biological Consequences" by H. Smith and J. W. Stather. National Radiation Protection Board, Harwell, U.K., November 1976.
10. Insoluble particles can remain in the lungs as long as 1000 days. Assuming the plutonium oxide is partially soluble, 500 days biological half-life is a reasonable assumption. See also ICRP #19.
11. Shipman, T. L. "A radiation fatality resulting from massive overexposure to neutrons and gamma rays." In: **Diagnosis and Treatment of Radiation Injury,** Geneva World Health Organization, p. 113, 1961.
12. Metivier, H. et al. "Excretion and Acute Toxicity of $^{239}PuO_2$ in Baboons." **Health Physics** 27:512, 1974.
13. Lisco, H. et al. "Carcinogenic Properties of Radioactive Fission Products and Plutonium." **Radiology** 49:361, 1947.
14. Bertell, R. "Environmental Influence on Immature Infant Survival: Wisconsin 1963-75." **International Perspectives in Public Health** 1:2, Fall 1984.

Section 3: Gastro-Intestinal Tract Dose

Radiation damage to the stem cells of the small intestine will impair their reproductive capacity. Mature cells will continue to migrate toward the tips of the intestinal villi, to be eventually sloughed off into the gut, without being replaced. If damage is severe enough to leave the villi bare of cells, i.e. 3 days without cell replacement, body fluids and electrolytes may leak into the gut depleting the body, and bacteria may invade the body from the gut. Either may cause death.

In the case of external radiation the stem cells of the gut and the major bone marrow deposits in the pelvic arch will be destroyed simultaneously. This will undoubtedly cause severe, interacting traumas. The gut syndrome will produce clinical signs first, however, because of the more rapid cell turnover. Death can occur in humans exposed to 2,000 rads (low LET) external radiation in 8 days. With localized doses of 1,000 rads, it is possible for some stem cell recovery both in humans and animals (1,2)

Animal experiments with internal beta emitters (averaging 1.4 MeV) energy delivering about 2,500 rads to intestinal stem cells exhibited two patterns of death: early death due to inability of stem cells to repopulate, and later death (after stem cell recovery) due to gross ulceration and fibrosis. Even though the stem cells recovered, the dogs suffered diarrhea and internal bleeding until death several months later (3). Both RSS-1975(4) and NRPB-1976 (5) based estimates of prompt fatalities on the analysis of this data on dogs. Neither analysis corrected the dose for tissue differences between human gut and dog gut. As noted previously, Metivier (6) has reported the baboon 4 times as sensitive to $^{239}PuO_2$ lung tissue dose than the dog. It is reasonably cautious to assume that lung and gut tissue (both epithelial) are similar, and that human tissue resembles baboon tissue more closely than dog tissue. For this reason the RSS-1975 suggested parameters for death from the gut syndrome were divided by a factor of 4. The LD_{50} is assumed to be 875 rads (low LET). with a range of 500 - 1,275. This is consistent with medical experience with therapeutic x-ray.

In the RSS-1975 analysis it was assumed that the integrated dose over the first 60 days determined the acute gut dose. This is inappropriate for an accident involving inhalation of insoluble Pu-239. As was noted by Cave and Ilberg (7), it is more conservative and more appropriate to integrate the dose over the first year.

RSS-1975 also assumed that an internal dose would be less damaging to lymph and blood vessels than external radiation would be, thereby increasing the probability of recovery. This may have been appropriate in a light water reactor accident, but is not appropriate for one involving insoluble actinides. For example, Park et al. (8) have shown that as long as 11 years after inhalation of $^{239}PuO_2$ about 40% remains in the thoracic lymph nodes. No increase in mortality rate due to this retention factor is assumed in the Handbook analysis, which implies that these mortality estimates may be too low.

Recovery from gut syndrome depends on general health, medications, availability of medical care, quality of radiation and duration of exposure. Persons with impaired health prior to the accident may respond negatively to much lower radiation dose levels.

Tracer studies, using ^{106}Ru, have documented significant differences between passage of material through the gastro-intestinal tract of neonatal vs. adult rats (9). The differences are both quantitative, reflecting physiological changes in relation to age, and qualitative, reflecting morphological differences. No research on the differences between infant and adult responses to gastro-intestinal tract radiation damage and dose distributions resulting from inhalation and/or ingestion of radioactive chemicals is available. However, in a a later paper, Sikov noted that gut-absorption of plutonium in the neonatal rat and dog was about 100-fold greater in neonatals than adults. There is also evidence of increased absorption of intact proteins from the G-I tract in humans during the neonatal period (10). This factor would be expected to reduce the radiation dose to gut, but increase whole body dose from ingestion. There is also evidence of a 20-fold absorption of plutonium bound to protein, as in milk, in children.

It can be generally concluded that passage of insoluble radionuclides through the gut is slower for the neonatal, causing increased dose to stem cells. Damage to stem cells is also increased because of the relatively smaller size of the neonatal intestine. It seems best to reduce the parameters for radiation related deaths due to gut irradiation by at least a factor of 10 for children under 10 years of age, and a factor of 100 for the embryo or fetus.

Table 4

MORTALITY DUE TO IRRADIATION OF THE G.I. TRACT

Study	Dose Integrated over	LD_{50}	Range	Comments
Sullivan-1976 (3) (Beagle Dogs)	Until Death	LD_{100}:2,500		
RSS-1975 (4) (based on animal experiments)	60 days	3,500 rads	2,000-5,000 rads low LET	Not corrected for dog to human tissue
NRPB-1976 (5) adopted from RSS	7days	3,500 rads low LET	2,000-5,000 rads low LET	Not corrected for dog to human tissue
RHP-1977 (7)	1 year	3,500 rads low LET	2,000-5,000 rads low LET	Not corrected for dog to human tissue
Handbook	1 year	875 rads low LET	500-1275 rads low LET	
children <10 years	1 year	90 rads low LET	50-130 rads low LET	

REFERENCES

1. Saenger, E. L. et al. "Whole Body and Partial Body Radio-therapy of Advanced Cancer." **American Journal Roentgenology** 117: 670. 1973.
2. Conard, R. A. et al. "Experimental Therapy of the G. L. Syndrome Produced by Lethal Doses of Ionizing Radiation." **Journal Applied Physiology** 9: 227.
3. Sullivan, M. F. et al. "Acute Toxicity in Rats and Dogs of Ingested Promethium-147 and Ruthenium-106," in: **Pacific Northwest Laboratory Annual Report for 1975** BNWL-2000 p. 97. 1976.
4. Reactor Safety Study: An Assessment of Accident Risks in U.S. Commerical Power Plants, Appendix VI. U.S. Nuclear Regulatory Commission, WASH-1400. 1975
5. Smith, H. and Stather, J. W. "Human Exposure to Radiation Following the Release of Radioactivity from a Reactor Accident: A Quantitative Assessment of the Biological Consequences." National Radiation Protection Board. Harwell, U.K. November 1976.
6. Metivier, H. et al. "Excretion and Acute Toxicity of $^{239}PuO_2$ in Baboons." **Health Physics** 27:512. 1974.
7. Cave, L. and Ilberg, D. "Relative Hazard Potential — The Basis for Definition of Safety Criteria for Fast Reactors." February 1977.
8. Park, J. et al. "Progress in Beagle Dog Studies with Transuranium Elements at Battelle-Northwest," **Health Physics** 22:803. 1972.
9. Sirkov, M. R. et al. "Comparison of Passage of a Tracer through the Gastrointestinal Tract of Neonatal and Adult Rats." **Growth** 33:57-68.
10. Sirkov, M. R. and Mahlum, D. D. "Plutonium and the Developing Animal." **Health Physics** 22: 707-712. 1972.

NOTES ON USING THE SECTION ON DEATHS DUE TO ACUTE EXPOSURE TO IONIZING RADIATION

Appropriateness: Exposure to the whole body or bone marrow in excess of 150 rem, to lung or gut in excess of 500 rem, within a short period of time can result in radiation related deaths to the normal healthy person. For the chronically ill, elderly and infants there are no direct estimates of radiation dose which would delvier a mortal blow. The ability to recover varies with their physical state. Exposure of an embryo or fetus in excess of 10 rem within a short period of time can result in embryonic, fetal or infant death.

Sample Question 1: If 2.3 million people were exposed to an average dose of 300 rem gamma radiation to the whole body in a major accident, how many would be expected to die within the first year after the accident due to the acute effects of exposure?

Answer: Using Table 1, page 4, one notes that the threshold for mortality response is probably no lower than 150 rem and no higher than 330 rem for healthy adults. If the threshold is 330 rem, there will be no casualties due to acute response to exposure. This does not, of course, rule out other physical damage or cancer.

If the threshold is 150 rem and the dose at which 50% would die (LD_{50}) is 350 rem, one would expect:

$$50\% \div 200 \text{ rem} = 0.25\% \text{ per rem}$$

increase in mortality above the 150 rem threshold. The reported exposure is 150 rem above the threshold.

$$150 \text{ rem} \times 0.25\% \text{ per rem} = 37.5\%,$$

which would be the expected mortality rate. In a population of 2.3 million, an upper bound on deaths due to acute exposure would be:

$$2.3 \times 10^6 \times 0.375 = 862{,}500 \text{ people.}$$

Again, using Table 1, the reader will note that 10 rem is the threshold for mortality response in the embryo or fetus, with a 50% lethal dose of 80 rem.

$$50\% \div 70 \text{ rem} = 0.71\% \text{ per rem,}$$

is the mortality rate above the 10 rem threshold. The 100% lethal dose is 150 rem, 140 rem above threshold (Note: this is in good agreement with experimental findings reported on page 2).

A population of one million has an annual birth rate of roughly 14,000, with about 10,500 women pregnant in any one day.

$$2.3 \times 10{,}500 = 24{,}150 \text{ pregnancies,}$$

would be expected in any one day in a population of 2.3 million. All of these pregnancies would be expected to result in reproductive loss during pregnancy or infant mortality.

Sample Question 2: In an accident, a group of 8 nuclear workers inhaled a radioactive gas. It was estimated that they received a lung dose of 3,000 rads. Will any of the workers die from this acute lung damage?

Answer: Using Table 3, one notes that the threshold for mortality response is 2,500 rads and the 50% lethal dose is 4,000 rads, 1,500 rads above the threshold.

$$50\% \div 1{,}500 \text{ rads} = 0.03\% \text{ per rad}$$

is the expected mortality rate above the 2,500 rad threshold. The exposure reported is 500 rads above threshold, therefore

$$500 \text{ rads} \times 0.03\% = 15\%$$

of the workers would be expected to die of acute lung irradiation, or

$$8 \times 0.15 = 1.2 \text{ workers.}$$

Given statistical fluctuations, one or two workers might die. The remaining workers although they recover from the acute damage would suffer from lung fibrosis and be at risk for other long range health problems.

Sample Question 3: In a laboratory accident a researcher accidentally swallowed plutonium. It was estimated that she suffered a 50 rad dose to stomach and intestines. Would she be expected to recover from this accident?

Answer: Since plutonium is an alpha emitter, high linear energy transfer (LET), the rad dose should be multiplied by 20 to give the comparable low energy transfer (LET) dose.

$$50 \times 20 = 1{,}000 \text{ rad low LET}$$

Using Table 4, page 8, one notes a threshold mortality of 500 rads, and a 50% lethal dose of 875 rads, 375 rads above the threshold.

$$50\% \div 375 \text{ rads} = 0.13\% \text{ per rad}$$

is the increase in mortality per rad exposure above the threshold. The woman researcher received 500 rads above the threshold, and has:

$$500 \text{ rads} \times 0.13\% = 65\%$$

probability of dying from the acute gut damage. With heroic medical care she might survive.

SECTION II

LIFETIME RISK OF RADIATION INDUCED CANCER

LIFETIME RISK OF RADIATION INDUCED CANCER

Until recently the estimates of long term health effects of exposure to radiation were based primarily on atomic bomb studies and research on ankylosing spondylitis patients. Newer studies and reviews, including the present, use a wide variety of research to obtain cancer site specific estimates. The general trend in estimates of total number of cancer induced in a population of one million people exposed to 1 rem ionizing radiation can be seen in the following table:

Table 5

LIFETIME RISK OF RADIATION INDUCED CANCER
IN A POPULATION OF ONE MILLION PEOPLE
EXPOSED TO A ONE REM DOSE

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 1977)	100
U.S. National Academy of Science (BEIR III 1980)	
- Limited to 11-30 years after exposure	719
John Gofman, **Radiation and Health** (Sierra Club Press - 1981)	3,333 to 4,255
Rosalie Bertell (1982)	
- Limited to 11-30 years after exposure	369 - 823
- Lifetime Cancers	549 - 1,648

The last three entries, which are up to 42 times higher than the UNSCEAR estimate, are based on observed cancer induction rates for specific organs. The BEIR III estimate is truncated, eliminating those cancers like leukemia and lymphoma which can begin to occur two to six years after the exposure, and the large number of cancers which occur more than forty years after exposure. It cannot be said to contradict the Gofman and Bertell estimates.

Table 6 gives the parameters used to derive the lifetime cancer risks given in Table 7. The Bertell 1982 cancer estimates in Table 5 are broken down into age at time of exposure, sex and tumor site in Table 7. The derivation of each estimate by cancer site is given on the subsequent pages.

The following terms are used in Table 6:

Latency: This is the number of years between exposure to ionizing radiation and the actual clinical diagnosis of the cancer. Sometimes it is the same as the time between exposure and death, either because of short survival time after diagnosis or because the cancer was detected at autopsy. Since not all cancers are fatal, the broader (first) definition is used in the Handbook.

> **Example 1:** A radiation induced liver cancer in a man exposed to radiation at age 37, would normally not be clinically detectable until he was 47 years or older, i.e., after a ten year latency period.
>
> **Example 2:** A woman 20 years old exposed to breast irradiation would not be expected to have a clinical observable radiation induced breast cancer until she was over 35 years of age. Had she been over 25 years at the time of the exposure, the latency period would be expected to be 10 years instead of 15 years.

Duration of Risk: The risk of radiation induced cancer in an exposed population continues for this length of time after the latency period expires.

> **Example 1:** A male exposed to thyroid irradiation at age 12 will be at risk from radiation induced thyroid nodules between ages 22 and 52. It is assumed that the risk from the adolescent exposure is essentially zero after age 52.
>
> **Example 2:** Children treated with radiation therapy for tinea capitis (ringworm of the scalp) at age 8 are at risk for brain cancer after age 13 years. It is not known if the risk endures only to age 43 years, or for the child's lifetime.

Person Years: The number of persons times the number of years at risk. This is often abbreviated to PY or WY (woman years).

Entries in Table 7 are derived from Table 6 as follows:

Example 1: Males between ages 0-9 years at the time of thyroid exposure are expected to develop thyroid cancer at a rate of 1 - 1.6 per million per year per rad exposure. The risk begins after a latency period of 10 years and continues for 30 years.

$$(1 \times 10^{-6} \text{ per yr. per rad}) \times 1 \text{ rad} \times 30 \text{ yrs.} \times 10^{6} \text{ persons} = 30 \text{ cancers.}$$

$$(1.6 \times 10^{-6} \text{ per yr. per rad}) \times 1 \text{ rad} \times 30 \text{ yrs.} \times 10^{6} \text{ persons} = 48 \text{ cancers.}$$

Hence among a million males exposed to one rad thyroid irradiation between ages 0 and 9, 30 to 48 would be expected to develop thyroid cancer during their lifetime. The reader will note on Table 8 that in a population of one million with mixed ages, 7% or 70,000 would be males 0-9 years of age. Hence if one was predicting thyroid cancers for males 0-9 years of age in a mixed age population of one million exposed to a one rad thyroid dose, these estimates would be multiplied by 0.07:

$$0.07 \times 30 = 2.1 \text{ cancers,}$$
$$0.07 \times 48 = 3.4 \text{ cancers.}$$

Example 2: Males over 50 years of age at the time of thyroid exposure are assumed to have an average age of 58 years. The ten year latency period for this cancer makes them 68 years of age, (that is at the limit of the assumed 68 year life expectancy) prior to clinical manifestation of the disease. Chances are these males would die of some other cause before being diagnosed with thyroid cancer.

Example 3: A million women between ages 10 and 19 years exposed to one rad ionizing radiation to breast tissue would be at risk of breast cancer after a 16 to 25 year latency period, for 30 years to life. The upper and lower estimates of breast cancer for this group would be:

$$(6.6 \times 10^{-6} \text{ per yr. per rad}) \times 1 \text{ rad} \times 30 \text{ years} = 198 \text{ cancers,}$$
$$(27.7 \times 10^{-6} \text{ per yr. per rad}) \times 1 \text{ rad} \times 38 \text{ years} = 1{,}050 \text{ cancers.}$$

The expected lifetime beyond age 35 for women is assumed to be 38 years.

In a mixed age population of one million 7.5% would be women between ages 10 and 19 years. The estimate of breast cancers for this age group of women becomes:

$$198 \times 0.075 = 15 \text{ cancers}$$
$$1{,}025 \times 0.075 = 77 \text{ cancers.}$$

Example 4: Women over 50 years of age exposed to one rad ionizing radiation to the breast tissue would have a lower breast cancer expectancy than younger exposed women because of their shorter remaining life span. If the average age of this group is 59, the number of years duration of risk is 3 beyond the 10 year latency period.

$$(4.7 \times 10^{-6} \text{ per year per rad}) \times 1 \text{ rad} \times 3 \text{ years} = 14.1 \text{ cancers,}$$
$$(12.3 \times 10^{-6} \text{ per year per rad}) \times 1 \text{ rad} \times 3 \text{ years} = 36.9 \text{ cancers.}$$

In a mixed age population this age group of women is about 16% of the total. The estimated number of breast cancers in women over 50 years at the time of exposure per million people of mixed ages exposed to 1 rad ionizing radiation would be:

$$14.1 \times 0.16 = 2.3 \text{ breast cancers}$$
$$36.9 \times 0.16 = 5.9 \text{ breast cancers}$$

The reader will note that although breast cancer induction rate for all age groups of women over 20 years is assumed to be the same on Table 6, Table 7 reflects different actual incidence rates for the various age groups due to the relatively shorter life expectancy of women over 50 years of age. This difference is sometimes used to justify mammography screening in women over 50 years of age at the time of exposure.

Table 8 gives the expected numbers of each cancer type in a population of one million people of mixed ages and sex, based on European and North American experience. The proportion assumed for each age and sex subgrouping is the percentage given in Table 10. A comparable estimate using different percentages can easily be constructed.

With the last row of Table 7, marked Weighted Sums gives the total number of cancers expected in each age and sex group in a population of one million persons of mixed age.

Table 6

CANCER RISK ESTIMATES
PER 10^6 PERSON YEARS/RAD LOW LET EXPOSURE

SITE	LATENCY (years)	DURATION OF RISK (years)	AGE AT EXPOSURE 0 - 9	10 - 19	20 - 34	35 - 49	50+
Thyroid - Male	10	30	1 - 1.6	1 - 1.6	1 - 1.6	1 - 1.6	1 - 1.6
Female	10	30	3 - 4.7	3 - 4.7	3 - 4.7	3 - 4.7	3 - 4.7
Nodules - Male	10	30	3 - 4.8	3 - 4.8	3 - 4.8	3 - 4.8	3 - 4.8
Female	10	30	9 - 14.1	9 - 14.1	9 - 14.1	9 - 14.1	9 - 14.1
Lung	After 35 or 10	30 to life	0.75 - 7.5	0.75 - 7.5	0.86 - 2.58	2.98 - 8.94	5.10 - 51
(High LET)*					(17.2 - 51.6)	(59.5 - 178.5)	(102 - 1,020)
Breast - Female	After 35 to 10	30 to life	6.6 - 27.7	6.6 - 27.7	4.7 - 12.3	4.7 - 12.3	4.7 - 12.3
Liver	10	30 to life	13.3 - 22.2	6.5 - 11.1	1.3 - 2.2	1.3 - 2.2	1.3 - 2.2
(High LET)*					(26.1 - 44.3)	(26.1 - 44.3)	(26.1 - 44.3)
Leukemia	2	25	1 - 3.4	1 - 2.2	1 - 2.2	1 - 2.2	1 - 2.2
Esophageal	After 35 to 10	30 to life	0 - 0.39	0.06 - 0.39	0 - 0.39	0.21 - 0.39	0.39 - 1.80
Stomach	10	30 to life	1.3 - 2.6	—	1.6 - 3.2	5 - 10	.5 - 1
Intestine & Rectum	10	30 to life	0.1 - 1.7	0.1 - 1.7	0.1 - 1.7	0.1 - 1.7	0.1 - 1.7
Pancreas	6	30 to life	0.83 - 8.3	0.83 - 8.3	0.83 - 30**	0.83 - 30**	0.83 - 8.3
Pharynx, Hypo-					or 0.83 - 30	or 0.83 - 3	
pharynx & Larynx	20	30 to life	0.5 - 1.0	0.5 - 1.0	0.5 - 1.0	0.5 - 1.0	0.5 - 1.0
Salivary Gland	15	30 to life	0.05 - 0.10	0.05 - 0.10	0.05 - 0.10	0.05 - 0.10	0.05 - 0.10
Lymphoma	2	25	0.1 - 0.4	0.1 - 0.3	0.1 - 0.3	0.1 - 0.3	0.1 - 0.3
Renal & Kidney	After 45 or 10	Life	0.13 - 0.34	0.13 - 0.34	0.13 - 0.34	0.13 - 0.34	0.13 - 0.34
Ovary - Female	6	30 to life	1.67 - 2.39	1.67 - 2.39	1.67 - 2.39	1.67 - 2.39	1.67 - 2.39
Uterus and							
Cervix Uteri	5	30 to life	0.5 - 0.5	0.5 - 0.5	0.5 - 0.5	0.5 - 0.5	0.5 - 0.5
Bone -							
Endosteal Dose	4	20	0.01 - 0.07	0.01 - 0.07	0.01 - 0.07	0.01 - 0.07	0.01 - 0.07
(High LET)*	(4)	(20)	(0.27 - 1.33)	(0.27 - 1.33)	(0.27 - 1.33)	(0.27 - 1.33)	(0.27 - 1.33)
Bone -							
Av. Skeletal	4	20	0.1 - 0.5	0.1 - 0.5	0.1 - 0.5	0.1 - 0.5	0.1 - 0.5
(High LET)*	(4)	(20)	(2 - 10)	(2 - 10)	(2 - 10)	(2 - 10)	(2 - 10)
Paranasal Sinuses							
& Mastoid Air	20	30 to life	0.8 - 0.8	0.08 - 0.24	0.08 - 0.24	0.08 - 0.24	0.08 - 0.8
(High LET)	(20)	(30 to life)	(16 - 16)	(1.6 - 4.8)	(1.6 - 4.8)	(1.6 - 4.8)	(16 - 16)
Brain	5	30 to life	4.4 - 6.1	4.4 - 6.1	4.4 - 6.1	4.4 - 6.1	4.4 - 6.1
Skin (White)	10	Life	0.4 - 4.4	0.4 - 4.4	0.4 - 4.4	0.4 - 4.4	0.4 - 4.4
(High LET)*					(2.9)	(2.9)	

* High LET was measured directly. When this measurement was used to estimate low LET carcinogenicity, it was divided by 20 (ICRP 26)
** Nuclear workers

Table 7

LIFETIME RISK OF CANCER PER 10^6 PERSONS OF THE INDICATED AGE AND SEX AT TIME OF EXPOSURE WITH 1 REM (10mSv) EFFECTIVE DOSE EQUIVALENT OF IONIZING RADIATION

Site	Age of Time of Exposure									
	0 - 9 yrs		10 - 19 yrs		20 - 34 yrs.		35 - 49 yrs.		50+ yrs.	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Thyroid Cancer	30 - 48	90 - 141	30 - 48	90 - 141	30 - 48	90 - 141	16 - 26	60 - 94	—	9 - 14
Nodules	90 - 144	270 - 423	90 - 144	270 - 423	90 - 144	270 - 423	48 - 77	180 - 282	—	27 - 42
Lungs	22 - 255	22 - 255	22 - 255	22 - 285	26 - 83	26 - 93	48 - 143	60 - 179	—	15 - 153
Breast	—	198 - 1,050	—	198 - 1,050	—	141 - 443	—	94 - 246	—	14 - 37
Liver	390 - 1,200	390 - 1,290	195 - 488	195 - 533	39 - 71	39 - 80	21 - 36	26 - 44	—	4 - 7
Leukemia	25 - 85	25 - 85	25 - 55	25 - 55	25 - 55	25 - 55	25 - 55	25 - 55	7 - 15	11 - 24
Esophageal	0 - 13	0 - 15	2 - 13	2 - 15	0 - 12	0 - 14	3 - 6	4 - 8	—	1 - 5
Stomach	39 - 140	39 - 151	—	—	48 - 102	48 - 115	80 - 160	100 - 200	—	2 - 3
Intestine and Rectum	3 - 92	3 - 99	3 - 75	3 - 82	3 - 54	3 - 61	2 - 27	2 - 34	—	0 - 5
Pancreas	25 - 481	25 - 515	25 - 398	25 - 432	25 - 108	25 - 120	13 - 60	17 - 72	2 - 25	2 - 36
(Nuclear Workers Upper Limit)					(1,080)	(1,200)	(600)	(720)	(249)	(357)
Pharynx, Hypopharynx and Larynx	15 - 44	15 - 48	15 - 34	15 - 38	11 - 22	13 - 26	5 - 10	5 - 10	—	—
Salivary Gland	2 - 5	2 - 5	2 - 4	2 - 4	1 - 3	2 - 3	1 - 2	1 - 2	—	—
Lymphoma	2 - 10	2 - 10	2 - 8	2 - 8	2 - 8	2 - 8	2 - 7	2 - 8	1 - 2	1 - 3
Renal and Kidney	4 - 12	5 - 13	3 - 8	4 - 10	3 - 8	4 - 10	2 - 5	3 - 7	—	0 -1
Ovary	—	50 - 148	—	50 - 124	—	50 -96	—	40 - 57	—	12 - 17
Uterus and Cervix Uteri	—	15 - 32	—	15 - 26	—	15 - 20	—	12 - 13	—	4
Bone (Skeletal)	2 - 10	2 - 10	2 - 10	2 - 10	2 - 10	2 - 10	2 - 10	2 - 10	0 -2	1 - 4
Paranasal Sinuses and Mastoid Air	24 - 35	24 - 38	3 - 11	3 - 12	3 - 8	3 - 9	1 - 4	2 - 5	—	2 - 3
Brain	132 - 360	132 - 384	132 - 299	132 - 323	132 - 226	132 - 250	92 - 128	110 - 152	18 - 24	35 - 49
Skin	22 - 238	23 - 255	18 - 194	19 - 211	13 - 141	14 - 158	6 - 70	8 - 88	—	1 - 13
Sum for non-nuclear workers	827 - 3,172	1332 - 4,970	569 - 2,040	1,070 - 3,780	453 - 1,100	904 - 2,130	368 - 826	752 - 1,560	28 - 69	143 - 421
Sum for nuclear workers					(453 - 2,070)	(904 - 3,210)	(368 - 1,370)	(752 - 2,210)	(28 - 292)	(141 - 741)

N.B. Table entries are to the nearest integer, with three significant figures or less.

Table 8

TOTAL NUMBER OF CANCERS EXPECTED OVER A LIFETIME WITH A SINGLE DOSE OF 1 REM (10 mSv) TO A POPULATION OF 10^6

Cancer Site	Expected Number of Ca.
Thyroid: Cancer	38 - 60
Nodules	115 - 182
Lung	25 - 150
Breast	55 - 228
Liver	97 - 275
Leukemia	20 - 48
Esophageal	1 - 9
Stomach	33 - 79
Intestine and Rectum	2 - 44
Pancreas	16 - 177
Pharynx, Hypopharynx and Larynx	8 - 19
Salivary Gland	1 -2
Lymphoma	2 - 6
Renal and Kidney	2 - 6
Ovary	18 - 38
Uterus and Cervix Uteri	6 - 8
Bone	2 - 8
Paranasal Sinuses and Mastoid Air	5 - 10
Brain	93 - 186
Skin	10 - 113
	549 - 1,648

* Age and sex distribution assumed to be typical of Europe or North America, as indicated on Table 9.

Table 9

LIFETIME CANCER RISK OF 1 REM (10mSv) BY SITE - ALL AGES AND SEXES COMBINED, IN A POPULATION OF 10^{6}*

Site	Years After Exposure 0 - 10	11 - 30	30+	
Thyroid: Cancer	—	28-45	10-15	38-60
Nodules	—	86-135.3	29-46.3	115-182
Lung	—	18-78	7-72	25-150
Breast	—	26-76	29-152	55-228
Liver	—	66-113	31-162	97-275
Leukemia	8-18	12-30	—	20-48
Esophageal	—	1-4	0-5	1-9
Stomach	—	28-57	5-22	33-79
Intestine & Rectum	—	1-24	1-20	2-44
Pancreas	3-24	11-70	2-83	16-177
Pharynix, Hypopharynx and Larynx	—	3.4-7	4.3-12	8-19
Salivary Gland	—	1	0-1	1-2
Lymphoma	1-2	1-4	—	2-6
Renal & Kidney	—	1-2	1-4	2-6
Ovary	3-5	12-18	3-15	18-38
Uterus & Cervix Uteri	1	4	1-3	6-8
Bone (skeletal)	1-3	1-5	—	2-8
Paranasal Sinuses and Mastoid Air	—	2-4	3-6	5-10
Brain	21-30	61-84-6	11-71.6	93-186
Skin	—	5.6-61	4.7-52	10-113
	38-83	369-823**	142-742	549-1,648

ASSUME 22% TO 30% NON-FATAL

* Age distribution assumed to be typical of Europe or North America, as indicated on Table 10.

** BEIR III (1980) estimate for this category is 719.

Table 10

TOTAL NUMBER OF CANCERS EXPECTED OVER A LIFETIME WITH A SINGLE DOSE OF 1 REM (10 mSv) TO A NORMALLY DISTRIBUTED POPULATION OF 10^6 * WITH THE STATED AGE AT TIME OF EXPOSURE

Age	Male		Female		Combined	
	Ca. per 10^6	Proportion	Ca. per 10^6	Proportion	Ca. per 10^6	Proportion
0-9	827-3,172	7%	1,332-4,967	7%	1,080-4,070	14%
10-19	569-2,044	7.5%	1,074-3,782	7.5%	822-2,913	15%
20-34	453-1,103	10%	904-2,135	10%	678-1,619	20%
35-49	367-826	10%	753-1,566	10%	560-1,196	20%
50+	28-68	15%	141-420	16%	86-250	31%
All	378-1,168	49.5%	717-2,119	50.5%	549-1,648	100%

* Normal age distribution for Europe and North America. This table can be easily adjusted to suitably describe the lifetime risk for populations with different age and sex distributions.

Table 11

TOTAL NUMBER OF CANCERS EXPECTED OVER A LIFETIME FOR NUCLEAR WORKERS WITH EFFECTIVE DOSE EQUIVALENT 1 REM (10 mSv) IN A POPULATION OF 10^4

Age	Male		Female	
	Ca. per 10^4	Proportion	Ca. per 10^4	Proportion
20-34	4.53 - 20.75	50%	9.04-32.15	50%
35-49	3.67 - 13.66	40%	7.53-22.14	40%
50+	0.28 - 2.92	10%	1.41-7.41	10%
All	4-16	100%	8-26	100%

N.B. For nuclear workers the highest credible estimate includes the observed rate of pancreatic cancer among Hanford nuclear workers. This rate was divided by ten for estimate of pancreatic cancer in the general public since two non-occupationally exposed populations exhibited lower rates.

EXAMPLES OF USES OF TABLES 6 THROUGH 11

Sample Question 1: In an nuclear accident, insurance liability only begins when members of the general public receive doses above 25 rem. Assume that an accident occurred in which 1.7 million people were exposed to an average dose of 15 rem to the whole body. No one exceeded the 25 rem dose. How many members of the public would be expected to develop radiation induced cancers not compensated for by the insurance?

Solution: The weighted sums for all ages, both sexes and all cancer sites in Table 8 would be used. Since these numbers were calculated per rem dose, per million people, they need to be increased to fit the given accident situation.

$$(549 \times 10^{-6} \text{ per rem}) \times 1.7 \times 10^{6} \times 15 \text{ rem} = 14{,}000$$
$$(1{,}648 \times 10^{-6} \text{ per rem}) \times 1.7 \times 10^{6} \times 15 \text{ rem} = 42{,}024$$

Between 14,000 and 42,024 cancers would be expected.

Sample Question 2: Assume that 70,000 males about 30 years of age were X-rayed, using a procedure which delivered an average 0.5 rem dose to active bone marrow. How many leukemias might be induced by this procedure?

Solution: Using Table 7, one notes that 25 to 55 leukemias would be expected to be induced in a million males exposed to one rem ionizing radiation between ages 20 and 34 years. This is adjusted to fit the given situation:

$$(25 \times 10^{-6} \text{ per rem}) \times 7 \times 10^{4} \times 0.5 \text{ rem} = 87.5 \times 10^{-2} = 0.9$$
$$(55 \times 10^{-6} \text{ per rem}) \times 7 \times 10^{4} \times 0.5 \text{ rem} = 192.5 \times 10^{-2} = 1.9$$

One would expect one or two radiation induced leukemias in the group of 70,000 men.

Sample Question 3: A labor union is examining its contract with an employer. The union has 800,000 members handling radioactive materials. The contract covers only those health effects reported within 5 years of the suspected exposure date. Workers are all male, they average 1 rem per year exposure, and they have been working an average of ten years. How many radiation induced cancers in this group are potentially reportable within 5 years of the exposure? How many are not potentially reportable within 5 years because of the long latency period for development of the cancer?

Solution: Assume the male workers are between ages 20 and 50, with 400,000 in each of the two age groups. Equal size groups are assumed since 10% of the general population is in each age group. Using the sum for all cancers at the bottom of the two male age columns on Table 7 as estimated for nuclear workers:

$$[(453 \times 10^{-6} \text{ per rem}) \times 4 \times 10^{5} \times 10 \text{ rem}] + [(367 \times 10^{-6} \text{ per rem}) \times 4 \times 10^{5} \times 10 \text{ rem}] = 3{,}280 \text{ cancers}$$
$$[(2{,}070 \times 10^{-6} \text{ per rem}) \times 4 \times 10^{5} \times 10 \text{ rem}] + [(1{,}370 \times 10^{-6} \text{ per rem}) \times 4 \times 10^{5} \times 10 \text{ rem}] = 13{,}760 \text{ cancers}$$

The radiation exposure to date would be expected to induce between 3,280 and 13,760 cancers. Using Table 6, one notes that those cancers with less than 5 year latency period are: leukemia, lymphoma and bone cancer. Assuming the cancer expression will be equally probable during any year after the latency period and within the time of allowable reporting:

Leukemia: $3 \div 25 = 0.12$ will be detectable per 10^6
Lymphoma: $3 \div 25 = 0.12$ will be detectable per 10^6
Bone (skeletal): $1 \div 20 = 0.05$ will be detectable per 10^6

Therefore the cancers which would be reportable within 5 years of the radiation exposure which induced them would be:

Leukemias:

$$(25 \times 10^{-6} \text{ per rem}) \times 8 \times 10^{5} \times 10 \text{ rem} \times 0.12 = 24 \text{ cases}$$
$$(55 \times 10^{-6} \text{ per rem}) \times 8 \times 10^{5} \times 10 \text{ rem} \times 0.12 = 52.8 \text{ cases}$$

Lymphomas:

$$(2 \times 10^{-6} \text{ per rem}) \times 8 \times 10^{5} \times 10 \text{ rem} \times 0.12 = 1.92 \text{ cases}$$
$$[(8 \times 10^{-6} \text{ per rem} \times 4 \times 10^{5} \times 10 \text{ rem}) + (7 \times 10^{-6} \text{ per rem} \times 4 \times 10^{5} \times 10 \text{ rem})] \times 0.12 = 7.2 \text{ cases}$$

Bone (skeletal):

$$(2 \times 10^{-6} \text{ per rem}) \times 8 \times 10^{5} \times 10 \text{ rem} \times 0.05 = 0.8 \text{ cases}$$
$$(10 \times 10^{-6} \text{ per rem}) \times 8 \times 10^{5} \times 10 \text{ rem} \times 0.05 = 4 \text{ cases}$$

The number of cancers detectable before the 5 year cut off, calculated in this way would be between 27 and 64, or 0.4 to 0.5% of the total. Since the cancers are not usually evenly distributed over the entire duration time, and since other factors such as internal contamination may increase cancer incidence rate and delay onset time for bone cancers (due to slower dose rate) these numbers are only approximate. However they indicate a seriously outdated worker compensation regulation.

Sample Question 4: In Canada and most other countries the maximum permissible yearly dose to any individual from nuclear industries is 0.5 rem and the maximum average dose to a population per year is 0.17 rem. Assume that a TMI type accident gave an average exposure of 0.08 rem to a population of 2 million people. How many cancers would that radiation dose be expected to induce? How many would be induced had the permissible average dose of 0.17 rem been delivered to the population of 2 million?

Solution: Using the weighted total for all ages, both sexes and all cancer sites in Table 8:

$$(549 \times 10^{-6} \text{ per rem}) \times 2 \times 10^{6} \times 0.08 \text{ rem} = 88 \text{ cancers}$$
$$(1{,}648 \times 10^{-6} \text{ per rem}) \times 2 \times 10^{6} \times 0.08 \text{ rem} = 264 \text{ cancers}$$

Between 88 and 264 radiation induced cancers would be expected. The permissible average dose if reached in one year would be expected to induce:

$$(549 \times 10^{-6} \text{ per rem}) \times 2 \times 10^{6} \times 0.17 \text{ rem} = 187 \text{ cancers}$$
$$(1{,}648 \times 10\text{-}6 \text{ per rem}) \times 2 \times 10^{6} \times 0.17 \text{ rem} = 560 \text{ cancers}$$

between 187 and 560 cancers.

NOTE 1: In the actual TMI accident, 0.08 rem was estimated to be the maximum dose, not the average dose.

NOTE 2: The user of the Handbook will recognize that the value of estimates of cancer obtained from the Handbook depend on the accuracy of the input data. For example in **Sample Question 4** one must assume that the 0.08 rem average dose is to the whole body and being from an external gamma source, is uniformly distributed over all body organs and tissues. If the dose had been 0.08 rem skin dose from diagnostic medical X-ray, the dose to organs and soft tissue would be about 0.05 rem and the dose to bone marrow about 0.01 rem or less. This would significantly reduce the cancer estimates. Moreover in a nuclear accident situation there are ordinarily inhaled and ingested radioactive particles giving additional organ and tissue exposures not associated with medical X-ray. The more detailed the input information becomes the more precise the cancer estimates can be.

NOTES ON RISK ESTIMATES:

Cancer estimates have been based on the ionizing radiation dose to the specific organ in question. There are four components of this dose:

external penetrating radiation,

internal whole body dose from circulating radioactive chemicals,

localized dose from radioactive chemicals lodged in the specific organ,

dose to the specific organ from radioactive chemicals lodged in other internal sites in proximity to the site of concern.

For external highly penetrating gamma radiation, where dose to tissue and bone are equal and whole body exposure homogeneous, the table may be used as presented. For external "soft" X-radiation, where the tissue dose may be 9 to 10 times the dose to bone marrow, the doses at specific sites must be calculated. Combinations of internal and external exposures must be evaluated in terms of the four possible sources of exposure to each site.

The estimates may be considered reasonable lower and upper bounds based on currently available information. The spread of estimates reflects more the biological variations in population response to stress than error bounds for mathematical calculations. Another source of variation in estimates is availability of medical care. The pre-clinical cancer state is usually accompanied by immunological incompetence. The patient may die from infection before cancer is diagnosed. Because of the many still unanswered questions in radiobiology, especially for low dose, slow dose rate predictions, no mathematical error estimates can be made with confidence.

As noted previously, the Handbook estimates are for low Linear Energy Transfer (LET) radiation such as gamma, X and beta radiation. The International Commission on Radiological Protection (ICRP) has recommended that tissue dose in rads be multiplied by 20 for high LET radiation such as alpha particles to estimate internal rem dose to tissue (2). This may not be completely realistic, at times leading to overestimating, and at other times leading to underestimating the cancers. There is some evidence that the Relative Biological Effectiveness (RBE) of high LET versus low LET radiation increases as dose decreases (3,4). However, since the Hiroshima dosimetry for gamma radiation and neutrons is now being revised (5), and these RBE and risk factors were based on Japanese data, these estimates may be changed. A simple linear dose response with constant RBE was assumed in this paper. Until the radiobiology becomes clearer, it is the "best estimate" which can be given.

The research findings on which the risks for each site were calculated will be given separately. In general, the risks refer to the posibility of a radiation induced mutational change in cells leading to a tumor. Non-malignant tumors are included for some sites, for example, thyroid, and non-fatal malignant tumors are included. This is more important for sites such as the thyroid or skin, where only 4% and 1% of the malignant tumors, respectively, would be expected to be directly fatal.

There are biological, hereditary and environmental factors which may modify the numbers of human cancers directly attributable to ionizing radiation exposure. The proportion of persons in the population who are susceptible to cancer or who are sensitive to radiation would be expected to affect the total numbers of cancers. Subgroups of children (6) and adults (7), twenty-five and twelve times as susceptible to leukemia as the average person, have been identified. It also has been shown that persons who already suffer from radiation induced thyroid nodule disease have two times the probability of getting radiation induced thyroid cancer than do persons who have spontaneously occurring nodular diseases (8). This would indicate probability differences between populations previously exposed to radiation from medical or nuclear fission sources and those relatively unexposed prior to a radiological accident. None of these factors are taken into consideration directly for the proposed risk estimates.

As noted in information on appropiate site exposures, some risk factors were derived for male workers between 20 and 40. In this report, it was generally assumed that children, the elderly and the general public would be more vulnerable to radiation damage than were these healthy workers, and risk estimates for these other groups were increased.

The tumor risk estimate assumes a homogeneous distribution of the photon radiation or radioactive chemicals on the organ, tissue or whole body. The question of "hot particles" or "warm particles", where the doses are more concentrated, has never been scientifically resolved. This may introduce a systematic underestimation of tumors in the case of moderately increased localized doses (due to non-homogeneous distribution of the radioactivity) to some tissues of high sensitivity to radiation. Should the doses become too concentrated because of non-homogeneity, cell killing and cell sterilization may be the predominant localized effect and the tumor formation may be less than expected. The "best estimate" at this point in time seems to be the direct estimate assuming homogeneous distribution, where non-homogeneous distribution is well documented and estimates of the effect of non-homogeneity can be made.

Since all ionizing radiation exposure causes damage on the cellular level, and since this damage is, rarely if ever perfectly repaired, evaluation of the long term health effects of such damage necessarily involves judgments as to which effects are "of concern" to the general public. These value judgments were summarized by the U.S. National Academy of Science as follows (9):

> There is no **firm** evidence that exposure to ionizing radiation causes premature aging in man or that the associated increased incidence of carcinogenesis is due to general acceleration of aging. It may be concluded from the available data that ionizing radiation induces or accelerates **some but not all** diseases, depending on genetic susceptibility of the subject and exposure conditions. For doses of less than approximately 300 rads of low LET (or 15 rad high LET) the **principle** mechanism of **life shortening** is the induction or acceleration of neoplastic diseases. This conclusion is essentially in accord with that of the I.C.R.P., that the evidence of **life shortening**, from effects other than tumor induction is **inconclusive** and therefore cannot be used for quantitative risk estimates (2). The United Nations Scientific Committee on the Effects of Atomic Radiation has taken a similar position that,with the possible exception of high dose exposures,lifeshortening depends **almost** entirely on the induction of neoplasia (10). (emphasis added)

The confusion of terminology between "life-shortening" and "premature aging" should be obvious. Early occurrence of chronic debilitating old age diseases such as diabetes, arthritis or chronic ischemic heart disease reduces quality of life but is not necessarily "life-shortening".

Much of the difficulty with quantifying the non-cancer deaths due to radiation exposure has been over-reliance on atomic bomb survivor data, where the population was seriously depleted of the more fragile portion prior to the Life-Span Study population selection in 1950. Yet even using this inappropriate data base and inappropriate criterion, namely direct "life-shortening", there is an increased mortality between ages 50 and 70 among moderately exposed (40 - 179 rads) survivors for causes other than cancer.

Between 1962 and 1966 (17 to 21 years after the bombing) the following mortality pattern was reported (11):

Table 12

A-BOMB MORTALITY 1962-66

	Observed	Expected	O/E
Infective and parasitic diseases	19	17.6	1.08
Allergic, endocrine, metabolic and nutritional diseases	15	9.3	1.61
Diseases of blood and blood-forming organs	5	2.4	2.08
Diseases of nervous system and sense organs	101	82.6	1.22
Diseases of circulatory system	59	49.7	1.19
Diseases of the respiratory system	16	17.8	0.90
Diseases of the digestive system	21	22.4	0.94
Senility, symptoms and ill-defined conditions	21	20.1	1.04
Other diseases	17	14.4	1.18

This excess was primarily confined to the age group over 52, i.e. those who were over 35 at the time of bombing, and the moderately exposed group.

In a 1978 publication of the Radiation Effects Research Foundation (the new name for the Atomic Bomb Casualty Commission at Hiroshima and Nagasaki) it is stated:

> Among Hiroshima males under age 10 at the time of bombing the survival rate seems to be somewhat below that for the O rad group starting around 1970 (when they had reached ages 25 to 35). The difference is not yet statistically significant...the effect of low radiation dose may soon become more evident.
>
> The most prominent feature of the survival curves is the apparent radiation effect for the population under age 10 at the time of bombing. In both cities and in both sex groups the survival rates for those exposed to 100 rad or more (Kerma) have, after a latent period, dropped below those for the control groups. The number of deaths in this age group is still small and consequently the survival rates are high, however, the differences in proportion of the original cohorts alive at the end of 1976 between the 100 rad or more group and the control group is statistically significant (12).

These deaths are from all causes, including but not limited to cancers.

General "life shortening" effects of radiation are certainly not well understood at this time, and the evidence is just beginning to be available. One may also legitimately question the scientists' right to assume that "life shortening" is the only effect "of concern" to the public.

Confirming data on non-cancer deaths was frequently discounted by the researchers because the rate of deaths did not always show increase in the highest dose category of atomic bomb exposure victims. This does not necessarily imply a lack of relationship with exposure. In the highest dose category a much greater proportion of victims died prior to the selection of the Study Population in 1950, hence the highest exposure group was selected for extraordinary hardiness. It is presumed that "frailty" was an important factor in early mortality. It is also likely that the high tumor induction in this highest exposure group later took precedence as a first cause of death. Both of these factors are confounding variables with respect to measurement of non-cancer deaths.

Diabetes among Hiroshima males was the only non-cancer death category which showed linear trend with dose as a cause of death (11).

An indirect measure of aging, namely the ratio of soluble to insoluble collagen in various extracts, showed a dose response relationship among A-bomb survivors (14). Collagen change represents the single most reliable chemical indicator of the aging process, and it is altered characteristically with normal aging (15).

There is a growing body of literature associating radiation exposure and heart disease (see attached partial bibliography). The decision to limit radiation health effect research and estimates to cancers, and even more restrictively to **fatal** cancers, appears to be more political than scientific.

It seems important in general, therefore, to point out that non-cancer debilitating chronic illness may well pose serious long term problems to populations exposed to a nuclear reactor accident. Damage to the immune system and blood (aplastic anemia) may lead to premature death due to infectious disease (16). These illnesses are not included in the Risk Table.

The further question about cancers accelerated by exposure to ionizing radiation is also important. Such health effects are not covered by the Risk Table, which includes only radiation **induced** cancers. An approach to measuring this acceleration of leukemia has been made (17) but comparable studies with respect to other cancers have not been undertaken due to lack of funding for such research. In general, at low doses of radiation one rad exposure from medical X-ray (0.1 rad bone marrow dose) increased non-lymphatic leukemia risk by the same amount as one year natural aging (0.1 rad bone marrow dose from natural background radiation). Atomic bomb studies have never been controlled for this aging effect of medical X-ray, although the Study Population, chosen in 1950, has been routinely X-rayed for various reasons since that time. The Atomic Bomb population has also not been anlyzed for aging on the specific leukemia related chronic diseases identified by means of the Tri-State Leukemia Survey (18). It again seems unrealistic for scientists to assume that the public is concerned only with radiation induced cancers and not with radiation accelerated cancers induced by aging or other environmental carcinogens. Other chronic diseases brought on prematurely by radiation exposure above background levels may also be of public concern.

The Risk Table may be considered a "best estimate" of the worst health effect, namely radiation tumor induction. In terms of human suffering however, the premature onset of debilitating diseases and the acceleration of cancers caused by other pollutants may have the greatest impact on public perception of the "costs" of a reactor accident.

REFERENCES

1. Vaupel J. W. et al. "The Impact of Hetergeneity in Individual Frailty on the Dynamics of Mortality" **Demography** Vol. 16 No. 3 (August 1979).
2. I.C.R.P.Publication #26. Pergamon Press 1977.
3. Rossi, H. H., and Kellerer, A. M., "The Validity of Risk Estimates of Leukemia Incidence Based on Japanese Data." **Radiation Research** 58: 131-140 (1974).
4. Rossi. H. H. and Mays, C. W. "Leukemia Risk from Neutrons." **Health Physics** 35: 353-360 (1978).
5. "Japanese A-Bomb Data will be Revised: DOE Conference marks the first step in a general overhaul of dose estimates; Academy of Science asked to help." **Science** Vol. 214, 2 October, 1981 pp. 31-32.
6. Bross, I. D. J. and Natarajan, N. "Leukemia from Low-level Radiation. Identification of Susceptible Children." **New England Journal of Medicine** 287: 107-110 (1972).
7. Bertell, R. "Radiation Exposure and Human Species Survival." **Environmental Health Review** 25: 43-52 (1981).
8. Schneider, A. B. et al. "Incidence, Prevalence and Characteristics of Radiation-induced Thyroid Tumors." **American Journal of Medicine** 64: 243-252 (1978).
9. BEIR II. "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation", 1980 p.505.
10. UNSCEAR "Sources and Effects of Ionizing Radiation" Report to the General Assembly. New York: United Nations 1977.
11. Beebe, G. W. et al. Studies of the Mortality of A-Bomb Survivors. 4. Mortality and Radiation Dose, 1950-1966 **Radiation Research** 48, 613-649 (1971).
12. Morijama, Iwao and Lillian Guralnick. "Survival Experience of Atomic Bomb Survivors, Hiroshima and Nagasaki, 1951-76" Technical Report RERF TR 17-18 (1978).
13. Stewart, Alice M. "Delayed effects of A-Bomb radiation: A review of recent mortality rates and risk estimates for five-year survivors." **Journal of Epidemiology and Community Health**, June 1982, Vol. 26, No. 2 pp. 80-86.
14. Anderson, R. E. et al. "Aging in Hiroshima and Nagasaki Atomic Bomb Survivors, Soluble-Insoluble Collagen Ratio." Technical Report 11-72).
15. Walord, R. L., M.D. **The Immunologic Theory of Aging** Publ. by Munksgaard Copenhagen. p. 176 (English Ed. by Williams and Williams Co. Baltimore).
16. Stewart, Alice M. and G. W. Kneale. "Non-Cancer effects of exposure to A-Bomb radiation." **Journal of Epidemiology and Community Health** 1984, Vol. 38.
17. Bertell, R. "X-ray Exposure and Premature Aging." **Journal of Surgical Oncology** 9: 379-391 (1977).
18. Viadana, E. "Use of Medical History to Predict the Future Occurence of Leukemias in Adults" **Preventive Medicine** 3: 165-170 (1974).

SPECIAL REFERENCES: RADIATION-INDUCED HEART DISEASE

1. Earl P. Benditt and John Benditt: "Evidence for a Monoclonal Origin of Human Atherosclerotic Plaques." Proceedings of the National Academy of Science. Vol. 70, No. 6, pp. 1753-1756, June 1973.
2. Arthur Elkeles, M.D. "Atherosclerosis and Radioactivity." **Journal of the American Geriatric Society**. Vol. 14, No. 9 pp. 895-901, Sept. 1966.
3. Arthur Elkeles, M.D. "Alpha-ray Activity in Coronary Artery Disease." **Journal of the American Geriatric Society** Vol. 16, No. 5, pp. 576-583, May 1966.
4. J. Borak, M.D. "Radiation Effects on Blood Vessels."
   Part 1: Erythema, Edema. **Radiology**. Vol. 38, pp. 481-492, April 1942.
   Part 2: Inflammation Degeneration; Suppression of Growth Capacity; Retrogression; Necrosis. **Radiology**. Vol. 38, pp. 607-617, May 1942.
   Part 3: Telangiectasis; Effect on Lymph Vessels. **Radiology**. Vol. 28, pp. 718-727, June 1942.
5. John P. Conomy, M.D., and Robert W. Kellermeyer, M.D. "Delayed Cerebrovascular Consequences of Therapeutic Radiation: A Clinicopatholigic Study of a Stroke Associated with Radiation-Related Carotid Arteriopathy." **Cancer**. Vol. 36, No. 5, Nov. 1975.
6. Arthur Elkeles, M.D. "Metabolic Behavior of Alpha-Ray Activity in Large Human Arteries: Relationship to Atherosclerosis." **Journal of the American Geriatric Society**. Vol. 25, No. 4, April 1977.
7. Earl P. Benditt. "The Origin of Atherosclerosis." **Scientific American**. Feb. 3, 1977.
8. J. Robert Stewart, M.D., and Luis F. Fajardo, M.D. "Radiation-Induced Heart Disease: Clinical and Experimental Aspects." Radiologic Clinics of North America. Vol. IX. No. 3, December 1971.
9. J. Robert Stewart, M.D., and Luis F. Fajardo, M.D. "Dose Response in Human and Experimental Radiation-Induced Heart Disease." **Radiology** 99: 403-408, May 1971.

INDIVIDUAL CANCER SITE ESTIMATES

Thyroid

Thyroid cancers are increased with increased thyroid-stimulating hormone (TSH), whether this is a primary factor or secondary to iodine deficiency or administration of goitrogens. When radiation exposure is added to this condition the cancer rate of a dose of 500 rads (to animals) increased from 6% to 50%. Suppression of TSH decreases the incidence of tumors. It would be impossible to estimate levels of TSH in a large population exposed to a reactor accident, but variations within the population would certainly exist.

There are also differences in tumorigenesis of external photon radiation (gamma or X-ray) and internal radiation from the relatively short lived Iodine 131. External photon radiation effect seems to be independent of thyroid function. Iodine 131 seems to be not homogeneously distributed in the thyroid, especially if it is functioning abnormally and this could lead to intense irradiation of functioning follicles. Iodine 125, with a longer residence time in the thyroid, has greater carcinogenic power than Iodine 131.

Irradiation of the thyroid can cause acute thyroiditis or hypothyroidism, as well as both benign or malignant tumors. The radiation induced tumors are not usually considered to be fatal.

Two studies, the University of Rochester Follow-up of those with Thymus Irradiation during Infancy (8) and the Children Irradiated for Tinea Capitis Study in Israel (9), indicate a higher sensitivity to radiation induced thyroid tumors among Jewish people. Females have about 3 times the incidence of thyroid tumors as males, and females of Jewish ethnic background have about 17 times the tumor rates of other children in the Rochester Study.

Risk estimates for thyroid irradiation are available for doses between 6.5 and 1,000 rads, for all ages and sexes, and for a variety of ethnic backgrounds. The risk estimate of four cases of thyroid malignancy per 10^6 person years per rad is central to these observed values. Benign thyroid adenoma or nodule induction is approximately 12 per 10^6 person years per rad. Since it is not known whether or not the peak incidence of thyroid tumors has been reached in Japanese or other studies, it is not certain whether this estimate seriously understimates the lifetime incidence rate. Two studies, the Japanese and Utah thyroid exposure analyses, seem to suffer serious methodological problems.

The Handbook choice of a ten year latency for thyroid tumors is based on the New York Tinea Capitis study. Benign tumors may occur before the ten year latency. A 30 year risk plateau is based on the Michael Reese study which observed peak incidence at 19 years after exposure. The Handbook parameters are based on a "best estimate" choice. It may underestimate the true risk.

Table 8

THYROID RISK ESTIMATES

Study	Findings	Comments
Un. Rochester (1) 2,872 exposed 5,055 siblings unexposed Irradiated thymus	Children in 1st year of life/20-35 year follow-up. 24 cases thyroid cancer observed, 0.29 cases expected. 3 cancers/10^6 person years/rad. 9 benign tumors/10^6 person years/rad.	Risk was 2.3 times higher in females. Risk was 17 times higher in Jewish females.
Un. of Chicago (2) 100 exposed 180 to 1,500 rad dose (average 750 rad)	Irradiation of head and neck at 4.5 years old. 26% had nodular thyroid disease, 7 were cancers. 4 cancers/10^6 person years/rad. 14.8 benign tumors/10^6 person years/rad.	No sex difference observed.
Michael Reese Hospital (3) 5,226 exposed (about 750 rad) 2,189 follow-up	90% were under 10 years when exposed. 5 cancers/10^6 person years/rad. 10 benign tumors/10^6 person years/rad.	Apparent peak incidence at 19 years after exposure
Tinea Capitis (Israel) (4) 10,902 Jewish children 6,000 sibling controls 10,900 tinea capitis non-irradiated controls	6.3 cancers/10^6 person years/rad. Benign tumors not reported.	10 cancer cases had estimated 6 to 9 rads. Risk was 3 times higher in females.
Tinea Capitis (N.Y.) (5) 2,215 exposed 1,395 controls with tinea capitis	Average age at irradiation 8 years. Follow-up 20 years (10 years after latency). 8 benign tumors with only 2 x 10^4 person years at risk. No cancers observed as yet.	6 - 10 rad dose.
U.S. Thyrotoxicosis Follow-up (6) 21,714 adults exposed 11,732 adults treated with surgery only 1,144 adults treated with antithyroid drugs only	16 cancers in patients treated with Iodine 131 (7.4 x 10^{-4}) and 11 in other therapy groups (8.5 x 10^{-4}).	Study was abnormal with respect to thyroid disease. No clear-cut findings.
Marshall Islands (7) 157 Islanders exposed atomic fall-out Adult dose 220-450 rad Child dose 700-1,400 rad	3.5 cancer/10^6 person years/rad. 20 benign tumors/10^6 person years/rad. (Only 22 year follow-up after exposure)	Majority of children with disease had most of thyroid tissue removed surgically. Little difference between adults and children.
Atomic Bomb (8) 17,000 exposed Dose levels being revised	1.89 cancers/10^6 person years/rad. Females 2.6 times higher than males.	Estimate artificially lowered because 5 years instead of 10 years latency was assumed.
Children downwind of Nevada Tests (9) 2,691 exposed (over 18 rad) 2,140 "minimally" exposed (under 18 rad)	No findings.	Studies by Utah Dept. Health were terminated before findings would have been expected to occur.

REFERENCES: Thyroid

1. Hempelman. L. H. "Thyroid Neoplasms Following Irradiation in Infancy", pp. 221-229 in **Radiation Associated Thyroid Carcinoma,** by L. J. DeGrott et al. Grune & Stratton, New York 1977.
2. Refetoff, S. J. et al. "Continuing Occurence of Thyroid Carcinoma after Irradiation to the Neck in Infancy and Childhood." **New England Journal of Medicine** 292: 171-175 (1975).
3. Schneider. A. B. et al. "Incidence, Prevalence and Characteristics of Radiation Induced Thyroid Tumors." **American Journal of Medicine** 64: 243-252, 1978.
4. Modan, B. et al. "Thyroid Neoplasms in a Population Irradiated for Scalp Tinea in Childhood", pp. 449-457, in **Radiation - Associated Thyroid Carcinoma,** ibid. Reference (1) 1977.
5. Shore, R. E. et al. "Follow-up Study of Patients Treated by X-ray Epilation for Tinea Capitis". **Archives Environmental Health** 31: 17-28, 1976.
6. Dobyns, B. M. "Radiation Hazard. Experience with Therapeutic and Diagnostic ^{131}Iodine", pp. 459-483 in **Radiation-Associated Thyroid Carcinoma,** ibid. Reference (1) 1977.
7. Conard, R. A. "Summary of Thyroid Findings in Marshallese 22 Years after Exposure", —. 241-257 in **Radiation-Associated Thyroid Carcinoma,** ibid. Reference (1) 1977.
8. Parker, L. N. et al. "Thyroid Carcinoma Diagnosed Between 13 and 26 after Exposure to Atomic Radiation." ABCC Technical Report TR5-73 (1973).
9. Rallison, M. L. et al. "Thyroid Disease in Children. A Survey of Subjects Potentially Exposed to Fallout Radiation." **American Journal of Medicine** 56: 457-463 (1974).

Lung Cancer

Most of the data on radiation related lung cancer comes from epidemiological studies of underground uranium or other heavy metal miners, fluorspar miners and hematite miners. In these situations, although a variety of environmental factors such as arsenic, uranium or fluoride were present, the constant relationship in all groups has been between exposure to radon gas and radon daughters and the incidence of lung cancer. In underground mines not associated with elevated concentrations of radon gas, such as the New Mexico potash mines, increased incidence of lung cancer has not been reported (1).

Estimates of lung cancer have been based on the studies of radon gas, and are usually measured in terms of Working Levels. One "Working Level" (WL) is defined as any combination of short-lived radon daughters (through polonium-214) leading to total emission of 1.3×10^5 MeV of alpha energy per liter of air. The cumulative measurement is the "Working Level Month" (WLM) defined as exposure at the rate of 1WL for 170 hours (8 hours/day, for 5 days/week, for 4.25 weeks). In order to estimate the rad dose to lung tissue from 1WLM exposure, one must take into account the thickness of the lung epithelial and mucous layers, factors known to vary with smoking and chronic bronchitis. In chronic bronchitis the mucous layer is thicker and the dose to the basal cell layer of the epithelium is lowered. Dose to the lung tissue is also affected by the fraction of radioactive ions free relative to the fraction bound to dust, to the breathing pattern of the individual (deep or shallow, rate per minute, etc.) and to whether the individual is a nose or mouth breather.

The conversion from WLM to rads was made on the assumption that 1WLM = 0.6 rads to lung tissue, with a range of 0.4 to 0.8 rads. The estimates used by the Handbook were based on the Czechoslovakian findings, which are central to other major estimates, divided into risks for age at exposure and based on long follow-up time. The adjustments for age distribution were made as follows:

Assuming 1WLM $\sim$ 0.6 rad to lung tissue:

$$\text{20 - 34 years: } \frac{0.67 \times 8.8}{0.6} + \frac{0.33 \times 13.3}{0.6} = 17.1/10^6\text{PY/rad}$$

$$\text{35 - 49 years: } \frac{0.33 \times 13.3}{0.6} + \frac{0.67 \times 46.7}{0.6} = 59.5/10^6\text{Y/rad}$$

These estimates were derived for workers with initial exposure prior to age 50 years. The Relative Biological Effectiveness (RBE) of radon and radon daughters for lung cancer relative to that of low LET X-radiation lies between 6.1 and 21.2, based on the Czechoslovakian data. Since 23 years may not be a long enough follow up of the exposed group to give a stable estimate of the lung cancers, the RBE for Swedish metal miners who were followed into retirement years was used. For this long follow-up, the RBE for alpha particles (radon daughters) is 20 (10,11). This is also the RBE recommended in ICRP Publication #26 (1977). There is also a probability that direct gamma irradiation from the ore body has affected uranium miner susceptibility to lung cancer, thus affecting RBE estimates. This would vary with ore and was not included in the Handbook estimate.

Since estimates of radiation induced lung cancers have been derived only for males hardy enough to be employed in manual labor in the mines, these values were adjusted to accommodate population variability. Assuming a linear increase with age, the estimate for persons over 50 years at time of exposure becomes 101.9 deaths/10^6PY/rad alpha. Dividing the three estimates by 20 gives the lower "best" estimates for the hardy members of the population used in the Handbook.

It was assumed, conservatively, that the non-mining male workers and women might be 3 times as vulnerable to radiation related lung cancer than were the miners between ages 20 and 49. Because of chronic illnesses and general health problems developing with age, it was also assumed that vulnerability among those over 50 years might vary by a factor of 10. These old age exposure estimates are theoretical, actually affecting primarily the females who have longer life spans, because of the long latent time for this cancer. No adjustment was made for non-homogeneous distribution of dose.

There are no estimates available for lung cancer risk in children. Those children exposed in Hiroshima, Nagasaki and the Marshall Islands are not yet old enough to begin developing this cancer. The cancer estimate for children is slightly less than that of the 20 - 34 year group because children are less exposed to smoking and other work place hazards. Since children's health may vary considerably and their ability to recover from radiological damage to lung tissue is unknown, it was conservatively estimated that their cancer induction rate might vary by a factor of 10.

The Handford estimate (9) raises two questions. The first concerns the relative biological effectiveness for cancers of low-radiation dose. This low dose effect is apparent in the U.S. Uranium miners (1), exposed to high LET alpha, and to the Hanford workers exposed to low LET gamma radiation. The Hanford problem may be complicated by inhalation of radio-active particles or other workplace carcinogens. The second question raised by the Hanford findings regards synergistic effects of whole body irradiation which might depress the immune system and accelerate the aging process at the same time as it initiates malignant processes in lung tissue. It is not clear at this time which of these possible biological mechanisms is operating. In view of these problems, the "best estimates" based on lung tissue exposure from radon and radon daughters may seriously underestimate the lung cancers caused by external gamma irradiation (low LET). The alpha radiation estimates may also be too low because the follow-up time of workers is still too short.

Table 14

LUNG CANCER RISK ESTIMATES

Study	WLM	Rad Dose to Lungs	Sex and Age at Exposure	Deaths/ 10^6PY/WLM	Deaths/ 10^6PY/rad
U.S. Uranium Miners 1920 - 1971 (2)	<360	<600	Male 20-50 yrs.	7.9	10.0-20.0 (alpha)
4,146 followed 14 years	>360	>600	Male 20-50 yrs.	3.5	4.4 - 8.8 (alpha)
Czechoslovakian Uranium Miners (3) About 4,000 followed 23 yrs.	<300	<500	Male 20-30 yrs.	8.8	11.0-22.0 (alpha)
			30-39 yrs.	13.3	16.6-33.2 (alpha)
			40+ yrs.	46.7	58.4-116 (alpha)
Canadian Uranium Miners (4) 15,094 followed 17 years	10.9	18.2	Male 20-50 yrs.	17.1	21.4-42.8 (alpha)
Newfoundland Fluorspar Miners (5) 2,414 miners	204	340	Male 20-50 yrs.	17.7	22.1-44.2 (alpha)
Swedish Metal Miners 1956-76 (6) 100 followed to old age	270	450	Male 20-50 yrs.	30.4	38.0-76.0 (alpha)
Ankylosing Spondylitis Patients (7) 14,554	—	197 (10 treatments over 4-6 weeks)	84% male 15-55 yrs.	—	2.8 low LET
A-bomb Survivors 19,472 (8)	—	86 (disputed)	Male &Female — all ages	— —	2.0 low LET (assuming a QF of 5 for neutrons
Hanford Workers 4,694 employees (9)	—	3	Male 20-50 yrs.	—	28 low LET

Summary of risk estimates per 10^6 Person Years per rad low LET exposure for lung cancer:

Age:	0-9	10-19	20-34	35-49	50+
Handbook	0.75 - 7.5	0.75 -7.5	0.86 - 2.58	2.98 - 8.94	5.10 - 51

REFERENCES: Lung Cancer

1. Lundin, F. E. et al. "Radon Daughter Exposure and Respiratory Cancer: Quantitative and Temporal Aspects." NIOSH-NIEHS Joint Monograph No. 1, U.S. Public Health Service. 1971.
2. BEIR III. The Effects on Population of Exposure to Low Levels of Ionizing Radiation: 1980. U.S. National Academy of Science. pp. 318-320. 1980.
3. Sevec, J. et al. "Lung Cancer in Uranium Miners and Long Term Exposure to Radon Daughter Products." **Health Physics** 30: 433-437. 1976.
4. Ham, J. M. Report of the Royal Commission on Health and Safety of Workers in Mines. Toronto: Ministry of the Attorney General, Province of Ontario. 1976.
5. Ibid, reference 2, pp. 322-324. 1980.
6. Axelson, O. and L. Sundell. "Mining, Lung Cancer and Smoking" **Scandinavian Journal of Work Environment and Health** 4:46-52, 1978.
7. Court Brown, W. M. and R. Doll. "Mortality from Cancer and Other Causes After Radiotherapy for Ankylosing Spondylitis" **British Medical Journal** 2: 1327. 1965.
8. Jablon, S. and H. Kato. "Radiation Dose and Mortality of A-bomb Survivors, 1950-1970." ABCC TR 10-71 Report No. 6. 1972
9. Kneale, G. et al. "Reanalysis of Data Relating to the Hanford Study of the Cancer Risks of Radiation Workers." IAEA Symposium on the Late Biological Effects of Ionizing Radiation. Vienna 13-17, March 1978 (Assumes $380/10^6$ lung cancers, 13.6 rad doubling dose).
10. Harley, N. H. and B. S. Pasternack. "Alpha Absorption Measurements Applied to Lung Dose from Radon Daughters." **Health Physics** 23:771. 1972.
11. Jacobi, H. S. "Relations Between the Inhaled Potential Alpha Energy of ^{222}Rn and ^{220}Rn Daughters and the Absorbed Alpha-Energy in the Bronchial and Pulmonary Region." **Health Physics** 23: 3. 1972.

BREAST CANCER ESTIMATES FOR WOMEN EXPOSED TO IONIZING RADIATION

The increased incidence of breast cancer in atomic bomb survivors and in women treated with radiation therapy because of TB or mastitis is well documented. However, interpretation of the findings and extension of these findings to other populations is difficult. For example, the natural incidence rates of breast cancer in Japan and the United States are quite different; hence the difference in response to radiation may be due to heredity, life style or environmental differences.

There is apparent agreement among researchers that the linear dose response is the "best" estimate for low dose, low LET, radiation exposure (1). There is no apparent difference in breast cancer rate when the dose is protacted rather than delivered in a short period of time. In fact, fractionation of dose may increase the proportion of adenocarcinomas relative to fibroadenomas, for the same cumulative radiation exposure (2). Because of this effect, protacted doses may be considered to have more serious consequences.

Although in the atomic bomb survivors there is evidence of an increased breast cancer rate in women exposed between ages 10 and 19 years, there is as yet little information on the women exposed between ages 0 and 9 years. Women who survived the atomic bomb, who were under 10 years in 1945, are now in their 40's, the age where breast cancer incidence begins to rise. The latest A-bomb report, covering years between 1950 and 1974, reported 5 breast cancers in this group (3). The total excess will not be known for another 30 years. The radiation therapy studies did not include any women in this very young age group.

The plateau for radiation related breast cancer incidence is at least 30 years, and may extend for a lifetime.

There is some discrepancy between A-bomb studies and therapy studies in absolute breast cancer increase for women 40 to 49 years old at the time of exposure. There was a deficit of cases in this age group among A-bomb survivors. There is some speculation about hormonal changes due to whole body exposure during menopausal years. However, this effect was not experienced by therapy patients. The A-bomb findings may reflect competing causes of death for women in this age group. (4).

The 1980 BEIR Committee estimated excess breast cancers using two models: A linear dose response model, and a linear dose response model assuming cell killing at higher doses (5). Cell killing reduces the expected number of cancers per rad at higher doses. For example, in the Massachusetts study of TB patients treated with fluoroscopy (6), those receiving a total dose less than 100 rad had higher cancer induction rate than those with a total dose above 100 rad.

For the Handbook, the lowest linear risk minus one standard deviation, and the highest linear risk (assuming cell killing) plus one standard deviation were used as lower and upper bound estimates. The chart compares these values with observed values in major breast cancer radiation studies. Handbook estimates are central to these empirical values.

Table 15

BREAST CANCER RISK ESTIMATES*

Study	<20 Yrs. at Exposure	>20 Yrs. at Exposures
A-Bomb Survivors (3)	9.0	0 to 4.9
N.Y. Mastitis Study (8)	27.9**	6.3 - 52.1*
Mass. TB Patients (7)	8.9	3.8 - 6.9
BEIR III Linear Estimate	10.4 ± 3.8	6.6 ±1.9
BEIR III Linear with Cell Killing Estimate	22.4 ± 5.3	8.7 ± 3.6
Handbook	6.6 to 27.7	4.7 to 12.3

* Per 10^6 Women Years per rad.
** Based on small numbers.

REFERENCES: Breast

1. BEIR III. "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980" U.S. National Academy of Science.
2. Dethlefson, L. A. et al. "Report of BCTF Ad Hoc Committee on X-ray Mammography Screening for Human Breast Cancer. Can Animal and In Vitro Studies Give New, Relevant Answers?" **Journal National Cancer Institute** 61: 1537-1545 (1978).
3. Tokunaga, M. et al. "Malignant Breast Tumors Among Atomic Bomb Survivors, Hiroshima and Nagasaki, 1950 - 1974." **Journal National Cancer Institute** 62: 589-597 (1979).
4. Stewart, A. M. "Delayed Effect of A-bomb Radiation: a review of recent mortality rates and risk estimates for five-year survivors." **Journal Epidemiology and Community Health**, June 1982, vol 36, No. 2 pp. 80-86.
5. BEIR III (see Ref. 1).
6. Boice, J. D .Jr., et al. "Risk of Breast Cancer Following Low Dose Exposure." **Radiology** 131: 589-597 (1979).
7. Boice, J. D. Jr. "Breast Cancer in Women After Repeated Fluoroscopic Examination of the Chest." **Journal National Cancer Institute** 59: 823-832 (1977).
8. Shore, R. E. et al. "Breast Neoplasm in Women Treated with X-rays for Acute Postpartum Mastitis." **Journal National Cancer Institute** 59: 813-822 (1977).

LIVER CANCER ESTIMATES FOR PERSONS EXPOSED TO IONIZING RADIATION

Estimates of liver cancer related to radiation exposure were given little attention until the studies of patients treated with Thorotrast became available in 1977 and 1978. Between 1928 and 1955 Thorostrast had been injected into patients suspected of brain diseases, as a contrast medium for X-rays. Follow-up studies of these patients in Germany (1), Denmark (2), and Portugal (3), revealed an increased rate of liver and gall bladder cancers 18 or more years after treatment. Similar treatment in the U.S. was associated with liver cancer increase after 12 years. This effect may be related to a chemical property of thorium which heightens the radiation effect.

The preliminary report on Handford Worker deaths (4) also noted liver and gall bladder cancer cases: 18 observed with 12.5 expected (standard mortality ratio 1.44) for males. The average cumulative radiation dose of these workers was quite low, 0.31 rad dose from external source. There were 2 liver cancers among female workers, making a total of 20 cases.

In addition to this new information on probable radio-sensitivity of liver tissue, there was also a discovery that humans retain in the liver 45% of the plutonium reaching the bloodstream, with a biological half-time there of 40 years (5). Prior to this discovery it was assumed that humans, like mice and rats, rapidly excreted plutonium and other actinides from the liver.

There is a discussion of the estimates of radiation induced liver cancer in the 1980 report of the U.S. National Academy of Science (BEIR III) (6). The Handbook has accepted the BEIR III lower risk estimate for liver cancer induction from alpha radiation exposure, assuming a 10 year latency lifetime risk, and "wasted" (redundant) radiation beyond latency prior to clinical diagnosis of disease:

$$26.1 \text{ liver cancers per } 10^6 \text{ person years/rad alpha}$$

The estimate of upper bound used by the Handbook is also taken from the U.S. National Academy of Science (BIER III) (6) report, estimating neutron effectiveness for liver cancer. The reason for using this external dose (high LET) estimate is to avoid the possible chemical toxicity problems specific to thorium which might have influenced the thorotrast estimates. Using Hiroshima dose estimates and observations of liver cancers assuming a 10 years latency and 30 year cancer expression after acute exposure, one obtains:

$$443 \text{ live cancers per } 10^6 \text{ person rads (neutron)}$$

This estimate might change with U.S. government adjustment of the neutron dosimetry (7).

Conversion of high LET effects to low LET effects was done by using the RBE of 20, as recommended in ICRP Publication #26 (1977). The risk for children under 10 years was assumed to be 10 times that of adults and the adult variability factor was assumed to be 3.

If the neutron dose at Hiroshima is re-assigned to low LET gamma, the estimates of liver cancers may be too low by at least one order of magnitude. The densely ionizing alpha particles may be a poor guide to low LET carcinogenicity because they cause excessive cell killing. Further studies of Hanford Workers would be advisable to resolve these problems.

Table 16

LIVER CANCERS RISK ESTIMATES

STUDY PER	CONDITIONS LINEAR	LIVER CANCERS 10^6 PY/rad	ENERGY TRANSFER
Germany Thorotrast	10 year latency 25 rads/person/year Not a lifetime risk	24.8	high
Denmark Thorotrast (2)	10 year latency 23 rads/person/year Not a lifetime risk	17.7	high
Portugal Thorotrast (3)	10 year latency 26 rads/person/year Not a lifetime risk	22.8	high
Thorotrast Studies combined	10 year latency 25 rads/person/year Not a lifetime risk	22.1	high
Thorotrast Studies combined and extended to life-	5 to 10 years dose prior to diagnoses considered "waste"	26.1 - 31.9	high
A-bomb survivors (6) - Neutron (No chemical toxicity)	Gamma ineffective to Gamma one-tenth as effective as neutron	23.1 - 43.3	high
Handbook	Adults (20 years)	26.1 - 44.3	high
Handbook	Under 10 years 10 -19 years 20 years or more	13.0 - 22.2 6.5 - 11.1 1.3 - 2.2	 low

REFERENCES: Liver Cancer

1. van Kaick, G. et al. "Malignancies in German Thorotrast patients and estimated tissue dose." **Health Physics** 35: 127-136, 1978.
2. Faber, M. "Malignancies in Danish Thorotrast patients." **Health Physics** 35: 153-158, 1978.
3. da Silva Horta, J. et al. "Malignancies in Portuguese Thorotrast patients." **Health Physics** 35: 137-152, 1978.
4. Mancuso, T. F. et al. "Radiation Exposure on Handford Workers Dying from Cancer and other Causes." **Health Physics** 33: 369 - 384, 1977.
5. ICRP Publication #19, p. 50. 1972.
6. BEIR III. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. 1980. U.S. National Academy of Science.
7. "Japanese A-bomb Data will be Revised" **Science** Vol. 214: 31-32, 2 October 1981.

LEUKEMIA INDUCED BY IONZING RADIATION

Leukemia increase in humans has been noted after radiation exposure in a variety of age-groups and nationalities, with various doses and dose-rates. Important studies include atomic bomb survivors (4), ankylosing spondylitis patients (5), children treated for tinea capitis (6), medical radiologist (7), thorotrast patients (3), persons given radium-224 treatments (8), radium dial painters (9), U.S. military men exposed to the nuclear bomb test named "Smokey" (10) and the Utah children downwind of the Nevada Test Site (11). Various estimates of cancer induction per person rad have been made and the Handbook has selected "best estimates" central to these measurements. Not all studies were suitable for an absolute leukemia induction value.

The Tri-State Leukemia Survey indicated that subgroups of children may be 25 times as susceptible to radiation-induced leukemia (12) and subgroups of adults 12 times as susceptible (13) as the norm. It would be necessary to estimate the size of the susceptible subgroup in a specific population in order to use these findings. Should they form a large proportion of the population, leukemia cases would occur at a significantly higher rate.

Other hematological conditions induced by radiation also occur: aplastic anemia (14), reduction in neutrophils (and hence resistance to infection and toxins) or reduction in lymphocytes and platelets (15). None of these health effects were included in the chart.

In a 1983 paper on cancers diagnosed within 22 years after exposure in the military population exposed at the Smokey Test (16), Glyn Caldwell withdrew his conclusion relative to radiation related leukemia reported in his 1980 paper (10). Participants in 200 other nuclear test have not been followed and their health effect experience is unknown.

Table 17

LEUKEMIA RISK ESTIMATES

Study	Conditions	Cases/10^6 PY/rad	LET
Nagasaki survivors (1)	Assumes 1 rad kerma is about 0.56 rad bone marrow dose low LET and 0.28 high LET	1.8 - 3.6	mixed
Hiroshima survivors (2)	RBE of 1 to 5 for neutrons	1.7 - 3.1	mixed
Thorotrast Patients (3)	Some labeled "myelophthisis" as cause of death were probably leukemia. Higher estimates include these	40 Up to 30 years after; lifetime risk will be higher)	high
A-bomb survivors (4)	Linear dose response for gamma and neutrons or linear-quadratic gamma and linear neutron models	1.0 - 2.2	low
Ankylosing Spondylitis Patients (5)	Average follow-up of 16.2 years	0.8	low
Children irradiated for tinea capitis (6)		3.4	low
Medical Radiologist (7)	Assumes accumulated bone marrow dose in lifetime was 240 to 600 rads; 35 years at risk	0.6 - 1.4 0.6 - 1.4	low low
Handbook	Under age 10 Over age 10	1 - 3.4 1 - 2.2	low low

REFERENCES: Leukemia

1. Beebe, G. W. et al. "Mortality Experience of Atomic Bomb Survivors: 1950-74." RERF Technical Report TR-1-77 (1978).
2. Ishimaru, et al. "Dose response relationship of neutrons and gamma rays to leukemia among atomic bomb survivors in Hiroshima and Nagasaki by type of leukemia." **Radiation Research** 77: 377-394, 1979.
3. Mole, R. H. "The Radiobiological Significance of the Studies with Radium 224 and Thorotrast." **Health Physics** 35: 167-174, 1978.
4. BEIR III. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980. U.S. National Academy of Science, p. 345.
5. Smith, P. G. and R. Doll. "Age and Time Dependent Changes in Rates of Radiation-Induced Cancers in Patients with Ankylosing Spondylitis Following a Single Course of X-ray Treatment." IAEA Report SM 224/711 (1978) pp. 205-218.
6. Albert, R. E. "Follow-up study of patients treated by X-ray epilation for tinea capitis." **Archives Environmental Health** 17: 899-918 (1968).
7. Matanowski, G. N. et al. "The current mortality rates of radiologists and other physician specialists. Specific causes of death." **Am. Journal of Epidemiology** 101: 199-210 (1975).
8. Spiess, H. et. al. "Soft tissue effects following 224 Radium injections into humans." **Health Physics** 35: 61-81 (1978).
9. Polednak, A.P. et al. "Mortality Among Women first employed before 1930 in the U.S. radium dial-painting industry." **Am. Journal of Epidemiology** 107: 179-195 (1978).
10. Caldwell, G. G. et al. "Leukemia among participants in military maneuvers at a nuclear bomb test." **Journal of American Medical Association** 244: 4 (1980) pp. 1575-1578.
11. Lyon, J. et al. "Childhood leukemia associated with fall-out from nuclear testing." **New England Journal of Medicine** 300: 8 pp. 397-402 (1979).
12. Bross, I. and Natarajan, N. "Leukemia from low level radiation: Identification of susceptible children." **New England Journal of Medicine** 287: 107-110, 1972.
13. Bertell, R. "Radiation Exposure and Human Species Survival." **Environmental Health Review** Vol. 25, No. 2 (1981).
14. Lewis, E. B. "Leukemia, multiple myeloma and aplastic anemia in American radiologists." **Science** 142: 1492-1494.
15. **Handbook of Radioactive Nuclides,** Yen Wand, Editor (Chem. Rubber Co.) pp. 849-854.
16. Caldwell, Glyn, et al. "Mortality and Cancer Frequency Among Military Nuclear Test (Smokey) Participants, 1957 through 1959" **Jr. American Medical Assoc.** Vol.250, No. 5 (Aug. 5, 1983).

CANCER OF THE ESOPHAGUS RELATED TO IONIZING RADIATION EXPOSURE

Table 18

ESOPHAGUS CANCER RISK ESTIMATES*

Study	0-9 yrs.	10-19 yrs.	20-34 yrs.	35-49 yrs.	50+ yrs.
A-bomb Survivors (rads Kerma) (1)	0	0.06	0	0.21	1.80
BEIR III (2) (for 11 to 30 yrs. after exposure)	0.07	0.07	0.13	0.21	0.56
Handbook	0-0.39	0.06-0.39	0-0.39	0.21-0.39	0.39-1.80

* Cancers per 10^6 PY/rad exposure

Esophageal cancers in excess of the expected number have been reported for both atomic bomb survivors in Hiroshima and for ankylosing spondylitis patients. There was no evidence of increased rate of esophageal cancer in Nagasaki and there was a question about the relationship between esophageal cancer and the underlying disease process for ankylosing spondylitis patients. Hence until recently this cancer was not considered to be induced by radiation.

The Nagasaki survivors tended to be younger than Hiroshima survivors. They were also subjected to less neutron dose. It may be too soon to see esophageal cancer in this smaller survivor population. The estimate of esophageal cancer for Hiroshima survivors is 0.39 cases/10^6 PY/rad exposure. This average was used by the Handbook as an upper estimate for cancers in persons under 50 years of age at time of exposure, and as a lower estimate for cancers in those 50 years or older.

The ankylosing spondylitis patients who received 250-500 rads as radiation therapy did not show an excess of esophageal cancer. However, in a recent study follow-up of those who had received only one X-ray therapy treatment, there were 9 cancers of the esophagus where only 4.27 were expected, 6 to 16 years after treatment (3). The excess is significant. The radiation dose is unknown but lower than the dose to the average patient who had multiple treatments. This appears to be a case of higher cancer induction rate at lower dose levels. Patients with ankylosing spondylitis who did not have radiation treatment did not show an increased rate of esophogeal cancer (4). Therefore the cancer is now presumed to be related to radiation rather than the underlying disease.

The Handbook estimates are based primarily on Hiroshima data and are not corrected for biased selection of hardy members of the population (survivors). They may understimate the cancer increase in a normal population.

REFERENCES: Esophagus

1. Beebe, G. W. et al. LSS Report 8. "Mortality Experience of Atomic Bomb Survivors 1950-74." TR 1-77 (1978).
2. BEIR III p. 198.
3. BEIR III p. 359.
4. Radford, E. P. et al. "Mortality among patients with ankylosing spondylitis not given X-ray therapy." **New England Journal of Medicine**. 297: 572-576 (1977).

STOMACH CANCER INDUCED BY EXPOSURE TO IONIZING RADIATION

Both the ankylosing spondylitis patients and the a-bomb survivors have experienced an excess of stomach cancer. No breakdown of age specific expected excess is available for ankylosing spondylitis patients and no common agreement on radiation dose to stomach tissue is available. However the values obtained in the ankylosing spondylitis study are important since the dose was from external X-ray exposure rather than the fission product ingestion experienced by a-bomb survivors in conjunction with external irradiation.

Table 19

STOMACH CANCERS PER 10^6 PY PER RAD LOW LET

Study	Conditions	Estimated excess cancers
Ankylosing Spondylitis (1)	Tissue dose estimate 60 rads, Dolphin and Eve (2)	2.68
Ankylosing Spondylitis	Tissue dose estimate 250 to 500 rads, BEIR I (3)	0.32-0.64
Ankylosing Spondylitis (4)	Update of cases, with 250 rads tissue dose assumed (1980)	0.59

The ankylosing spondylitis cases were almost all adults. The dose estimate changes the expected cancer rate by about a factor of four.

The Nagasaki data on stomach cancer is sparse, with a estimated 0 to 1.05 stomach cancer deaths per 10^6 person years per rad exposure.

Table 20

AGE SPECIFIC ESTIMATES OF EXCESS STOMACH CANCER ASSOCIATED WITH EXPOSURE TO IONIZING RADIATION PER 10^6 PERSON YEARS PER RAD

Study	0-9	10-19	20-34	35-49	Over 50
Hiroshima (5) by Kerma dose	0.56	—	0.71	2.22	0.23
Hiroshima by rad dose (low LET)	1.3	—	1.6	5.0	0.5
BEIR III Estimate (5)	0.40	0.40	0.77	1.27	3.35
Handbook	1.3-2.6	—	1.6-3.2	5-10	0.5-1

Lower limits used by the Handbook are consistent with a-bomb findings. These limits were doubled since the a-bomb survivors were artificially chosen for hardiness. These estimates may still be too low for a normally distributed population. If stomach cancer increase begins only after age 35, then the noted high lifetime rate in those 35-49 years at the time of bombing may have to be extended to the younger groups after they reach age 35. In those over 50 at the time of bombing, the competing causes of death together with the long latency period appears to be masking the cancer effect.

REFERENCES: Stomach

1. Court Brown, W. M. and R. Doll. "Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis." **British Medical Journal** 2: 1327-1332 (1965).
2. Dolphin, G. W. and I. S. Eve. "Some aspects of the radiological protection and dosimetry of the gastrointestinal Radiation Injury." Excerpta Medica Foundation Monograph. Nuclear Medicine and Biology No. 1, Amsterdam (1968).
3. BEIR I: The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. U.S. National Academy of Science 1972.
4. BEIR III (1980) p. 362.
5. Beebe, G. W. et al. LSS Report 8. "Mortality Experience of Atomic Bomb Survivors 1950-74." TRI-77 (1978).
6. BEIR III (1980) p. 198.

Table 21

CANCER OF THE INTESTINE AND RECTUM ASSOCIATED WITH IONIZING RADIATION

Study	Comments	Cancers per 10^6 PY/rad
Hiroshima (1) (to 1970)	Increase with increased dose to intestines	1.45 ± 0.67
Nagasaki (1) (to 1970)	Increase with increased dose to intestines	0.60 ± 0.45
A-bomb survivors combined, Female (to 1974)	Assumed RBE for neutrons of 15	0.30 ± 0.2
Ankylosing Spondylitis (2)	Assumes 57 rads to colon; Early excess cancers not included.	1.7 ± 1
BEIR III (3)	Colon cancer	0.26 to 2.23 (increasing with age)
Handbook	15 to 25 years after exposure	0.1 to 1.7

Many studies have shown an apparent excess of colon and rectum cancers with radiation exposure, especially in women. Studies include radium implants in women to induce artificial menopause (4), studies of women irradiated for pelvic disorders (5), follow-up of metropathia haemorrhagica patients treated with radiation (6,7), women treated with radium for cancer of cervix (8), radium dial painters (9) and the Nagasaki Tumor Registry. Not all of these studies can be quantified because of unknown radiation dose to the patient. The estimates used by the Handbook may prove to be too low because of selection of a-bomb survivors for hardiness and because the lifetime of the younger exposed group is not yet over. There are as yet no observations on this cancer development in those who were under 10 years at the time of exposure. They would now be about 45 years of age.

In studies of ankylosing spondylitis patients an excess of colon cancer during the first three years after exposure was noted, 6 vs. 2.52 expected. The number observed over the following six year was 6 vs. 4.39 expected. In ankylosing spondylitis patients not treated with radiation there were no excess cancers during the first 9 years after treatment. The excess early cancers may have been radiation promoted; i. e. they were subclinical at the time of radiation exposure and the radiation exposure interferred with the body's ability to destroy them or retard their growth. They were not counted in the estimate of radiation induced cancers. The Handbook estimates may prove to be too low, however, in a society where colon cancer rate is high and radiation promotion of the cancer may assume greater public health significance.

REFERENCES: Intestine and Rectum

1. Beebe, G. W. et al. LSS Report 8. "Mortality Experience of Atomic Bomb Survivors 1950-1974." TR1-77 (1978).
2. Fabrikant, J. I. and J. T. Lyman. Personal Communication to BEIR III, p. 369.
3. BEIR III, p. 198.
4. Brinkly, D. and J. L. Haybittle. "The late effects of artificial menopause by X-irradiation." **British Journal of Radiology** 42: 519-521 (1969)
5. Palmer, J. P. and D. W. Spratt. "Pelvic carcinoma following irradiation for benign gynecological diseases." **American Journal of Obstetrics and Gynecology** 72: 497-505 (1968).
6. Doll, R. and P. G. Smith. "The long term effects of X-irradiation in patients treated for metropathia haemorrhagica." **British Journal of Radiology** 41: 362-368 (1968).
7. Dickson, R. J., "Late results of radium treatment of carcinoma of the cervix." **Clinical Radiology** 23: 528-535 (1972).
8. Castro, E. B., et al. "Carcinoma of large intestine in patients irradiated for carcinoma of cervix and uterus." **Cancer** 31: 45-52. 1973.
9. Polednak, A. P. et al. "Mortality among women first employed before 1930 in the U.S. radium dial painting industry." **American Journal of Epidemiology** 107: 179-195 (1978).

Table 22

CANCER OF THE PANCREAS AND EXPOSURE TO IONIZING RADIATION

Study	Comments	Estimate of excess cases/10^6 PY/rad
Ankylosing Spondylitis (1)	Did not occur in non-irradiated patients	0.7 (0.2 to 1.4)
Atomic bomb survivors (2)	Pancreatic cancer poorly diagnosed in Japan.	0.83 ± 0.53 Nagasaki
Hanford Workers (3, 4)	Might be synergistic with chemicals; estimated for healthy workers at low dose rate	10
BEIR III (5)		0.24 - 1.97 (increasing with age)
Handbook	Adults 20-49 yrs.	0.83 - 3 general public 0.83 - 30 nuclear workers
	Children and Elderly	0.83 - 8.3

The trend toward increased cancer of the pancreas appeared in Nagasaki and to a much lesser extent in Hiroshima. However the Hiroshima tumor registry is known to be incomplete, therefore it was not considered for this estimate.

Pancreatic cancer was excessive in ankylosing spondylitis patients exposed to radiation therapy and not in those patients not treated with radiation. Hence this can be considered associated with radiation exposure rather than disease.

Pancreatic cancer was also reported in excess among women exposed to radiotherapy as a treatment for cancer of the cervix (6) or for lymphoma (7).

The Hanford worker estimate, which is high relative to the other estimates, measures cancer induction at low doses and slow dose rate. It is also an estimate for workers selected originally for above average health. It indicates that the other estimates based on populations depleted by a bombing or serious disease may understimate the problem (8).

The Handbook estimate reflects the large uncertainty in pancreatic cancer induction. For persons between 20 and 49 years of age at the time of exposure, the "best estimates" lie between the Nagasaki value of 0.83 cancers per 10^6 PY/rad, and 3 times the Hanford healthy worker estimate. The factor of 3 allows for population variability in frailty. Although the Hanford workers may have experienced a synergistic effect with exposure to some workplace chemical, there is no guarantee that the general public is not also subjected to chemical pollution as well as radiological pollution.

Because of these unknowns, the Handbook used three times the Hanford estimate for nuclear workers, and one-tenth of this estimate for the general public. This uncertainty affects only the best upper estimate.

The Handbook estimate is not unrealistically high for a normal population in an industrial country. Workplace hazards may well be present in the living space making the reduced estimate for the general public too low. The variability in individual frailty among the very young and those over 50 years was assumed to be such that predicted cancer rates might be too low by a factor of 10.

REFERENCES: Pancreas

1. Court Brown, W. M. and R. Doll. "Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis." **British Medical Journal** 2: 1327-1332 (1965).
2. Beebe, G. W. et al. LSS Report 8. "Mortality Experience of Atomic Bomb Survivors, 1950-74. TR1-77 (1978)
3. Mancuso, T. F. et al. "Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes." **Health Physics** 33: 5 pp. 369-384 (1977).
4. Kneale, G. W., T. J. Mancuso and A. M. Stewart. "Job Related Mortality Risks of Hanford Workers and Their Relation to Cancer effects of Measured Doses of External Radiation." In **Biological Effects of Low-Level Radiation,** pp.363-372, International Atomic Energy Agency, 1983, Vienna.
5. BEIR III p. 198.
6. Dickson, R. J. "Late results of radium treatment of carcinoma of the cervix." **Clinical Radiology** 23: 528-535 (1972).
7. Jochimsen, P. R. et al. "Pancreatic carcinoma as a sequel to therapy of lymphoma." **Journal of Surgical Oncology** 8: 461-464 (1976).
8. Steward, A. M. and G. W. Kneale. "Non-cancer effects of exposure to A-bomb radiation." **Jr. of Epidemiology and Community Health**, Vol. 38, 1984.

RADIATION RELATED CANCERS OF THE PHARYNX, HYPOPHARYNX AND LARYNX

The BEIR III report concludes that it is now recognized that there is a significantly increased rate of cancers of the pharynx in irradiated populations. The average latency period is about 25 years from the time of exposure and precise quantification of the lifetime risk is not yet available (1).

Some estimates are available but because of the long latency time and the imprecise dose estimates for therapy patients, these estimates have a high probability of being too low.

Table 23

EXCESS CANCER RISK ESTIMATES PER 10^6 PY/RAD

Study	Comments	Estimates
Ankylosing Spondylitis (2)	Patients only followed for 16 years; dose estimates vary from 250 to 880 rads	0.02 to 1.4
A-bomb Survivors (3)	Pharynx, hypopharynx, and larynx were not separately studied; 20 year follow-up only.	0.5 to 1.0
Handbook	Probably too low an estimate; a 20 year latency period was assumed which may also underestimate cancers	0.5 to 1.0

The Handbook estimate is the best available at this time, but is subject to revision upward.

Increases in cancer of the pharynx and larynx after radiotherapy were reported by Goolden (4), Rover and Levinson (5), Yoshizawa and Takeuchi (6), Kikuchi, et al (7) and Nitze (8). Radiation doses were in the therapeutic range but not precise enough for estimates of cancer per rad.

REFERENCES: Pharynx, Hypopharynx and Larynx

1. BEIR III pp. 389-392.
2. Court Brown, W. M. and R. Doll. "Mortality from Cancer and Other Causes after Radiotherapy for Ankylosing Spondylitis." **British Medical Journal** 2: 1327-1332 (1965).
3. Beebe, G. W. et al. L.S.S. Report 8. "Mortality Experiences of Atomic-Bomb Survivors, 1950-74." TR1-77 (1978).
4. Goolden, A. W. G. "Radiation Cancer. A Review with Special Reference to Radiation Tumors in the Pharynx, Larynx and Thyroid." **British Journal of Radiology** 30: 626-640 (1957).
5. Raven, R. W. and V. B. Levinson. "Radiation Cancer of the Pharynx." **Lancet** 2: 683-684 (1954).
6. Yoshizawa, Y. and T. Takeuchi. "Search for the Lowest Irradiation Dose from Literature on Radiation Induced Cancer in Pharynx and Larynx." **Nippon Acta Radiologica** 34: 903-909 (1974).
7. Kikuchi, A. et al. "Head and Neck Cancer Following Therapeutic Irradiation and Brief Review on Those in Japan." **Nippon Acta Radiologica** 34: 491-501 (1974).
8. Nitze, H.R. Radiogene Tumoren in H.N.O. Bereich Arch. **Klin. Ohren-Nasen-Kehlkopfheilk** 199: 634-638 (1971).

Table 24

SALIVARY TUMORS RELATED TO EXPOSURE TO IONIZING RADIATION

Study	Comments	Excess cases/10^6 PY/rad		
		Malignant	Benign	All Tumors
Saenger et al. 1644 infants & children (1)	Only 10-18 years follow-up (<600 R)	at least 0.1	—	—
Hempelman et al. 2,872 children (2)	Follow up 20 to 40 years	—	—	0.17-0.33
Janower and Miettinen 466 children (3)	More than 20 years follow-up (<400R)	—	—	at least 0.12
Albert et al. 2,215 children (4)	About 39 rads (5)	0.15	0.45	0.6 (0.05-1.75)
Modan et al. 10,902 children	15 year follow-up About 39 rads (5)	0.76	0.34	1.1
A-bomb survivors (7)	12 year follow-up	0.16	0.09	0.25 (0.08-0.67)
A-bomb survivors(8) (9) for Ref. (8)	19 year follow-up BEIR III estimate	—	—	0.05-0.11
A-bomb survivors (8)	Handbook estimate for Ref. (8) (Rad dose may be Kerma dose)	0.20 (21 at 135 rads; 6 at 32 rads)	0.03-0.10 (11 at 135 rads; 1 at 32 rads)	0.23-0.30
Handbook	same as BEIR III	—	—	0.05-0.10

Estimates of salivary gland tumors are quite imprecise at this point in time. The first three estimates given in the table are based on rad doses estimated very roughly. The Albert et al. (4) and Modan et al. (6) studies have more precise dosimetry but exposures are limited to children.

Studies of a-bomb survivors are complicated by imprecise knowledge of inhaled and ingested fission products. Dose estimates are for external radiation dose measured by distance from the hypocenter and shielding.

The Handbook accepted the very low estimates derived by BEIR III (9), without an age differential. The estimates may be too low for children by a factor of ten. They may be too high for adults. Little is known about latency period or the duration of risk for this cancer.

REFERENCES: Salivary Tumors

1. Saenger E. L. et al. "Neoplasia following therapeutic irradiation for benign conditions in childhood." **Radiology** 74: 889-904 (1960).
2. Hempelman, L. H. et al. "Neoplasm in persons treated with X-rays in infancy." Fourth Survey in 20 years. **Journal National Cancer Institute** 55: 519-530 (1975).
3. Janower, M. L. and O. S. Miettinen. "Neoplasms after childhood irradiation of the thymus gland." **Journal of the American Medical Association** 215: 753-756 (1971).
4. Albert, R. E. and A. R. Omran. "Follow-up study of patients treated by X-ray epilation for tinea capitis." **Archives of Environmental Health** 17: 899-918 (1968).
5. Harley, N. H. et al. "Follow-up study of patients treated by X-ray epilation for tinea capitis. Estimation of the dose to the thyroid and pituitary glands and other structures of the head and neck. **Physiology, Medicine and Biology** 21: 631-642 (1976).
6. Modan, B. et al. "Radiation induced head and neck tumors." **Lancet** 1: 277-279 (1974).
7. Belsky, J. L. et al. "Salivary gland neoplasms following atomic radiations." TR-23-72 ABCC-1972.
8. Belsky, J. L. "Salivary gland neoplasms following atomic radiation. Additional cases and reanalysis of combined data in a fixed population 1957-70." **Cancer** 35: 555-559 (1975).
9. BEIR III 1980.

Table 25

LYMPHOMA RELATED TO EXPOSURE TO IONIZING RADIATION

Study	Comments	Excess Cases/10^6 PY/rad
A-bomb survivors (1)	Occurred later than leukemia	12.5% leukemia rate 0.1
Ankylosing Spondylitis (2)	Assume disease originates in mediastinal lymph nodes	33.3% of leukemia rate 0.3
American Radiologists (3)	Assuming 150 rem exposure	0.13 - 0.16
U.S. uranium mill workers (4)	Assuming 17 years exposure at 10 times permissible level	0.1
Hempelmann et al. Infants (5)	8 cases (Note: 24 thyroid cancers were estimated to give $3/10^6$PY/rad cancers)	1
Handbook	Range of observed values with exception of high rate for children less than one year (5)	0.1-0.4 for 0-9 years 0.1-0.3 for 10+ years

The estimates for lymphoma used by the Handbook are one eighth of the Handbook leukemia estimates. This ratio is suggested by data from atomic bomb survivors. The range of values coincides with the observed range of values for radiation related lymphoma in the scientific literature.

REFERENCES: Lymphoma

1. Beebe, G. W. et al. LSS Report 8. "Mortality Experience of Atomic Bomb Survivors 1950-74." pp. 64-67. TR1-77 (1978).
2. Court Brown, W. M. and R. Doll. "Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis." **British Medical Journal** 2: 1327-1332 (1965).
3. Matanoski, G. N. et al. "The current mortality rates of radiologists and other physician specialists." **American Journal of Epidemiology** 101: 199-210 (1975).
4. Archer, V. E. et al. "Cancer mortality among uranium mill workers." **Journal Occupational Medicine** 15:11-14 (1973).
5. Hempelmann, L. H. et al. "Neoplasms in persons treated with X-rays in infancy. Fourth survey in 20 years." **Journal National Cancer Institute** 55: 519-530 (1975).

RENAL AND KIDNEY CANCER RELATED TO EXPOSURE TO IONIZING RADIATION

An excess of renal and kidney cancer related to radiation exposure has been noted in studies of thorotrast patients (1), metropathia haemorrhagica patients (2), patients treated for uterine cervix cancer (3), ankylosing spondylitis patients (4), and A-bomb survivors (5). Wenz (6) has reported a mean latency of 27.5 years for these tumors. A-bomb studies began to show a linear dose related increase in these tumors 22 to 25 years after the bombing.

The estimate of excess cancers per 10^6 PY per rad for Atomic Bomb Survivors Life Span Study is 0.13 (7). This value is used by the Handbook as a lower limit. In addition to the hardy survivor syndrome, the detection rate for cancers of urinary organs using death certificate information only is very low in the Japanese experience (8). Using City Tumor-Registry data, selected for A-bomb survivor information, estimates of 0.34 and 0.32 cases/10^6 PY/rad for Hiroshima and Nagasaki were observed. These estimates are also likely to be too low because of the hardy survivors effect. However, lacking better estimates the Handbook used 0.34 as an upper bound for cases/10^6 PY/rad. These estimates will no doubt need to be raised as further information becomes available.

REFERENCES: Renal and Kidney

1. da Silva Horta, J. et al. "Thorium dioxide effects in man. Epidemiological, clinical and pathological studies (Portugal)." **Environmental Research** 8:131-159 (1974).
2. Smith, P. G. and R. Doll. "Late effects of X irradiation in patients treated for metropathia haemorrhagica." **British Journal of Radiology** 49: 224-232 (1976).
3. McIntyre, D. and R. C. S. Pointon. "Vesical neoplasms occuring after radiation treatment for carcinoma of the uterine cervix." **Journal Royal College of Surgeons, Edinburgh** 16: 141-146 (1971).
4. Court Brown, W. M. and R. Doll. "Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis." **British Medical Journal** 2: 1327-1332 (1965).
5. Beebe, G. W. LSS Report 8. "Mortality Experience of Atomic Bomb Survivors 1950-74." TR1-77 (1978).
6. Wenz, W. "Tumors of the kidney following retrograde pyelography with colloidal thorium dioxide." **Annals N.Y. Academy of Science** 145: 806-810 (1976).
7. BEIR III (1980) p. 404.
8. BEIR III (1980) p.403.

CANCER OF THE OVARY IN WOMEN EXPOSED TO IONIZING RADIATION

The estimate for excess cancers of the ovary per 10^6 women years per rad is 1.67 ± 0.72, for a 12 year follow-up period after the assumed 10 year latency (1). Because of the problems of selection of healthy survivors with atomic bomb victims, the Handbook has adopted 1.67 and 1.67 + 0.72 = 2.39, as lower and upper estimates of cases per 10^6 women years per rad.

Excess ovarian cancers have been reported for women treated with radium or X-ray for uterine fibroids or benign pelvic disorders (2). However, the dose to the patients was unknown; therefore, estimates of excess per rad cannot be made.

As more data on this cancer becomes available, and as the younger atomic bomb victims reach mid-life, cancer of the ovary estimates may increase.

REFERENCES: Ovary

1. BEIR III (1980) p. 408.
2. Palmer, J. P. and D. W. Spratt. "Pelvic carcinoma following irradiation for benign gynecological diseases." **American Journal of Obstetrics and Gynecology** 72: 497-505 (1956).

UTERUS AND CERVIX UTERI CANCERS RELATED TO EXPOSURE TO IONIZING RADIATION

Unlike ovarian cancer, there are a few animal experiments to support the findings of increased uterine and cervix uteri cancers with radiation exposure. However, human experience with radiation therapy confirms a significant increase of these cancers with treatment (1). There is also an indication that in humans cancer induction per rad is higher at low doses than high doses (2).

Smith and Doll (3) reported an excess of 7 deaths per million exposed women per rad for a follow-up of 5 to 19 years after women were given 400 rads for therapeutic purposes. This gives an estimate of about:

$$0.5 \text{ cases}/10^6 \text{ WY/rad}$$

for fatal cancers. Non-fatal uterine cancer induction is undoubtedly much higher per rad, given present medical care and survival predictions for this cancer.

REFERENCES: Uterus and Cervix Uteri

1. Palmer, J. P. and D. W. Spratt. "Pelvic carcinoma following irradiation for benign gynecological diseases." **American Journal of Obstetrics and Gynecology** 72: 497-505 (1956).
2. BEIR III (1980) p. 410.
3. Smith, P. G. and. R. Doll. "Late effects of X irradiation in patients treated for metropathia haemorrhagica." **British Journal of Radiology** 49: 224-232 (1976).

BONE AND BONE RELATED CANCERS AFTER EXPOSURE TO IONIZING RADIATION

Like leukemia, bone sarcomas induced by radium 224 began to appear 4 years after exposure. Peak incidence rate was 6 to 8 years after and the epidemic appeared exhausted in 22 years. X-ray therapy has also been associated with bone sarcoma 4 to 27 years after exposure. However, bone sarcoma induced by ingested radium 226, which spreads homogeneously in bone and delivers a low chronic dose at slow rate appears to have a latency of 20 to 50 years after exposure.

Exposure to X-ray, radiation therapy and radium 226 or 228 tends to increase the rate of fibrosarcoma of the skeleton. Ra 224, wich has a much shorter residence time in the body and tends to stay on the surface of the bone, is associated with an excess of osteosarcoma. About 6 to 8% of the radiation induced malignant tumors are of a type which rarely if ever occurs naturally (1).

Bone sarcoma induction increases as the dose from radium 224 is fractionated and spread over a longer period of time (2).

The risk coefficient for Ra 224 is 40-200 bone sarcoma per 10^6 persons per rad for 4 to 27 years after exposure (3). The 200 estimate reflects protracted dose. This is roughly 2 to 10 cases/10^6PY/rad, the estimate used by the Handbook for bone cancer based on average skeletal dose from high LET radiation. This was related to 0.1 to 0.5 cases/10^6PY/rad low LET, using an RBE of 20 as recommended by ICRP #26.

Mays et al. (4) have estimated that the risk of bone sarcoma from radium 226 or radium 228, is 6 to 53 per million per rad endosteal dose, using the data of Rowland and Stehney (5). Assuming the duration of risk is 20 years, the best estimate of bone cancers is 0.3 to 2.65 per 10^6 PY/rad endosteal dose high LET radiation. Using an RBE of 20, this yields an estimate: 0.015 to 0.13/10^6 PY/rad low LET.

Because radium 226 and radium 228 spreads homogeneously in bone, the skeletal and endosteal dose are presumed to be the same. Radium 224, which stays on the surface of the bone, is thought to deliver an endosteal dose which is 7.5 times the average skeletal dose. Hence using radium 224 as a basis, one can estimate: 0.27 to 1.33 cases/10^6 PY/rad high LET for endoseal exposure. This is in rather good agreement with the observed value of 0.3 to 2.65 cases/10^6 PY/rad endosteal dose derived for radium 226 and radium 228.

REFERENCES: Bone

1. BEIR III, (1980) Table A-26 p. 416
2. Mays, C. W. et al. "Skeletal effects following Ra 224 injections into humans." **Health Physics** 35: 83-90 (1978).
3. BEIR III, (1980) p.414.
4. Mays, C. W. and H. Spiess. "Bone tumors in Thorotrast patients." **Environmental Research** 18: 88-93 (1979).
5. Rowland, R. E. and A. F. Stehney. "Exposure data for radium patients." pp. 177-231, Argonne National Laboratory Report ANL - 75 - 3 Part II (1974).

CANCER OF THE PARANASAL SINUSES AND MASTOID AIR CELLS AFTER EXPOSURE TO IONIZING RADIATION

U.S. radium dial painters contaminated with radium 226 are experiencing paranasal sinus and mastoid air cell cancers at times ranging from 19 to 52 years after their first exposure (1). There are no cases among German patients in 33 years follow-up since their exposure to radium 224.

Evans has proposed that these cancers are due to radon 222 gas, emanating from the radium 226 in bone (2).

Rowland et al. (3) have calculated the risk for this cancer as:

$$1.6 \text{ cases}/10^6 \text{ PY/rad to marrow free skeleton.}$$

This appears to be a risk for exposure to alpha particles, hence they are high LET. Cases have also been reported after thorotrast injections of maxillary sinuses for radiodiagnostic purposes (4).

Because the rate of cancer induction was based on female worker's experience, it was multiplied by three to give an adult population variation in frailty. Estimates were multiplied by 10 for children and elderly. Estimates were divided by 20 to obtain estimates for rads low LET.

In the case of a nuclear explosion or dispersion of fresh fission particles in a breeder reactor accident, this cancer may assume great public health significance because of the high energy alpha particles released.

REFERENCES: Paranasal Sinus and Mastoid Air Cell

1. Rowland, R. E. and A. F. Stehney. "Radium-induced malignancies." pp. 259-264. Argonne National Laboratory Report ANL-79-65 Part II (1978).
2. Evans, R. D. "The effects of skeletally deposited alpha-ray emitters in man." **British Journal of Radiology** 39: 881-895 (1966).
3. Rowland, R. E. et al. "Dose response relationships for female dial workers." **Radiation Research** 76: 368-383 (1978).
4. Mays, C. W. et al. "Skeletal effects following radium 224 injections into humans." **Health Physics** 35: 83-90 (1978).

Table 26

CANCER OF THE BRAIN ASSOCIATED WITH EXPOSURE TO IONIZION RADIATION

Study	Comments	Excess cases per 10^6 PY per rad
Stewart Case-Control 1,332 children (1)	Assumes in utero exposure of about 0.8 rad.	4.4 to 6.1 (BEIR III 1980)
MacMahon 120 CNS cancers in children (2)	In utero exposure. No indication of assumed dose.	6.3 to 11.2 (upper value is a crude risk)
Tinea Capitis - N.Y. 2,200 children exposed (3)	Average dose 140 rads to brain; follow-up av. 25 years	1.3
Tinea Capitis - Israel 10,900 children exposed (4)	Average dose 140 rads to brain (some 10% had two treatments)	0.2 to 2.2 (probably an under-estimate)
Michael Reese X-ray 5,166 X-ray therapy to head and neck (5)	Dose to brain not known.	14 tumor reported 1.6 expected
Handbook	Based on Stewart (1)	4.4 to 6.1

The estimate proposed by BEIR III for the Stewart analysis of the Oxford data (1) depends heavily on the rad dose estimate to the fetus. The dose used, 0.8 rad, was given in ICRP #24 (1970) and UNSCEAR (1958). The U.S. Department of Health Education and Welfare has estimated 0.595 rad dose from pelvimetry (1977) and a British estimate from 1957 was quoted in UNSCEAR 1972 as 0.238 rad. Dr. Karl Morgan assumed a 0.5 rad dose to the fetus per pelvimetry in his 1980 publication (6).

Using the 0.5 estimate, one would predict 7.04 to 9.76 cases per 10^6 PY per rad exposure to the fetus. Using the 0.283 estimate, one would expect 12.4 to 17.2/10^6 PY/rad to the fetus.

In addition to the tinea capitis patients, there are other examples of brain tumors reported after post natal irradiation. These include the research of A. J. Beller (7), J. Munk et al. (8) and R. Raskind (9). Radiation induced brain tumors in primates have also been reported (10, 11, 12). Hence this cancer is not just associated with pre-natal exposure. The Handbook has used the estimates based on Stewart's work at the higher assumed dose to compensate somewhat for fetal vs. post natal exposure cancer rates. In the absence of further information, this is a reasonable estimate.

REFERENCES: Brain

1. Bithell, J. F. and A. M. Stewart. "Pre-natal irradiation and childhood malignancy. A review of British data from the Oxford Survey." **British Journal of Cancer** 31: 271-287 (1975).
2. MacMahon, B. "Pre-natal X-ray exposure and childhood cancer." **Journal National Cancer Institute** 28: 1173-1191 (1962).
3. Shore, R. E. et al. "Follow-up study of patients treated by X-ray epilation for tinea capitis. Resurvey of post-treatment illness and mortality experience." **Archives of Environmental Health** 31: 17-28 (1976).
4. Modan, B. et al. "Radiation induced head and neck tumors." **Lancet** 1: 277-279 (1974).
5. Colman, M. et al. "Radiation induced tumors." IAEA Symposium, Vienna, March 1978. IAEA-SM 224-706 (1978).
6. Morgan, K. Z. "Hazards of Low Level Radiation" Yearbook of Science and the Future, Supplement of the Encyclopedia Britannica (1980).
7. Beller, A. J. et al. "The possible relationship between small dose irradiation to the scalp and intracranial meningiomas." **Neurochirurgia** 15: 135-143 (1972).
8. Munk, J. et al. "Radiation-induced intracranial meningiomas." **Clinical Radiology** 20: 90-94 (1969).
9. Raskind, R. "Central nervous system damage after radiation therapy." **International Surgery** 48: 430-441 (1967).
10. Kent, S. and J. Pickering. "Neoplasms in monkey (Macaca mulatta). Spontaneous and Irradiation induced." **Cancer** 11: 138-147 (1958).
11. Haymaker, W. et al. "Brain tumors in irradiated monkeys." **Acta Neuropathologica** 20: 267-277 (1972).
12. Traynor, J. and H. Casey. "Five-year follow-up of primates exposed to 55 MeV protons." **Radiation Research** 47: 143-148 (1971).

Table 27

SKIN CANCER RELATED TO EXPOSURE TO IONIZING RADIATION (CAUCASIANS)

Study	Comments	Excess cases/10^6 PY/rad
Tinea Capitis - N.Y. (1)	10 to 34 year follow-up; assumes 700 rads to the scalp	0.2 to 4.4 (1.02)
Hempelmann et al. (2)	Assume skin dose of 330 rads	0.1 to 1.5 (0.44)
Uranium miners (3)	Alpha dose 100 rads	2.9 (alpha)
Handbook		0.4 to 4.4

Since 5 of the tinea capitis patients were known to have received only 20 to 60 rads, and since treatment dose was 350 rads with higher doses occuring only where radiation fields overlapped, it seems more realistic to use 350 rads as the average dose to the scalp. This would increase estimates of skin cancers to 0.4 to 8.8 cases per 10^6 PY rad.

Hempelmann et al. reported 0.66 cases per 10^6 PY per rad for patients receiving less than 400 rads, and 0.32 cases per 10^6 PY per rad for those receiving more than 400 rads. Therefore it cannot be assumed that lower doses are less efficient for inducing this cancer. At doses of 1,300 rads fewer skin cancers than expected were observed (4). This is probably an indication that cell killing was extensive, reducing the probability of a viable carcinogenic cell surviving and reproducing.

Skin cancers induced by radiation show an increasing rate with age and with time after irradiation. There is a possibility of synergistic effect with ultra-violet radiation, especially for cancer of the face or neck. Radiation induced basal-cell cancers frequently manifiest multiple lesions, while this is rare in non-radiation related cancers.

It is thought that expression of skin cancer can occur at any time during the life of the exposed person. It has been known to occur as early as 1 year and as late as 64 years after exposure. Skin cancers are ussually not fatal and tend to be seriously underreported in vital statistics.

REFERENCES: Skin

1. Shore, R. E. et al. "Follow-up study of patients treated by X-ray epilation for tinea capitis." **Archives of Environmental Health** 31: 17-28 (1976).
2. Hempelmann, L. H. et al. "Neoplasms in persons treated with X-rays in infancy. Fourth survey in 20 years." **Journal National Cancer Institute** 55: 519-530 (1975).
3. BEIR III, p. 431 Unpublished data of M. Sercova, J. Sevc and J. Thomas (1980).
4. BEIR III, p. 431 Personal communication from Shore and Hempelmann. (1980).

SECTION III

GENETIC AND TERATAGENIC EFFECTS OF IONIZING RADIATION

GENETIC EFFECTS*

INTRODUCTION:

The normal human cell contains 46 paired chromosomes, 23 received from the father and 23 received from the mother. Each of the 23 chromosomes contains genetic information needed for the complex operation of the human body.

The 22 pairs of chromosomes called autosomes, are visibly different from one another in size, shape and staining property. They differ in function and individuals having only one chromosome of one pair or having three chromosomes of one pair either die prematurely or are grossly abnormal. Within the pairs, called homologues, the two chromosomes appear identical, although they may differ chemically at various sites called genes. If two chemicals at corresponding sites are identical, the person is said to be homozygous for that particular genetic trait. If two homologous chemical sites differ, the person is said to be heterozygous for that genetic trait and the question of dominance in effect arises. For example, if the child receives a gene for brown eyes from its mother, and a gene for blue eyes from its father, the child is said to be heterozygous for eye color. The child would have brown eyes because the action of the brown gene dominates. However if this brown eyed heterozygote marries another brown eyed heterozygote, some of their children will receive both genes for blue eyes, and be blue eyed homozygotes. The gene for blue eyes is said to be recessive. Most genes are considered partial dominants, having some effect on the individual. There are few completely recessive traits. Moreover, it usually requires several genes to produce one visible human trait such as hair texture and color.

The 23rd pair of chromosomes are usually called the sex chromosomes, and these are designated X and Y. Normally, the female has two X-chromosomes and the male has X and a Y chromosome. The Y-chromosome is thought to have very few genes. Damage to an X-chromosome is less serious for the female than for the male since the female may have a second normal X-chromosome to compensate. Some X-linked diseases or disabilities, such as hemophilia, are life threatening to males, while others such as color blindness are merely mild disabilities. Sex linked traits pass from father to daughter to son.

Humans reproduce by way of a highly intricate division of the primary reproductive cells, called spermatagonia and oocytes, into sperm and ovum. The process is called meiosis. In this process the primary reproductive cells with 46 chromosomes first pair the homologous chromosomes, and organize the pairs in such a way that one member of each pair goes to each of the two daughter cells produced. Each individual's sperm or ovum should contain 23 different kinds of chromosomes, with some originating from his or her mother and the rest from his or her father.

For sexual reproduction in humans, about 300 to 500 million sperms are deposited in the female vagina. The sperm travels to and penetrates a mature ovum, and the fertilized cell again has a full complement of 46 chromosomes. In a few rare cases, two sperm fertilize an ovum, giving 69 chromosomes. This usually results in embryonic or fetal death. If the individual survives to birth, it dies shortly thereafter and the trait is not passed on the next generation. Some triploid infants (69 chromosomes) are caused by faulty female meiosis resulting in an ovum with 46 instead of 23 chromosomes. These are, as stated previously, non-viable (1).

The total number of genes required for normal human development is not precisely known. Estimates range from about 25,000 to 100,000. Hence each of the 46 chromocomes contains roughly 500 to 2,000 genes.

FEMALES:

Development of primary germ cells is thought to begin around the 21st day of embryogenesis. These germ cells have a full complement of 46 chromosomes, and they reproduce themselves by mitotic division, i.e., each chromosome separates into two chromatids, one going to each of the two daughter cells, and each capable of producing its mirror image. The daughter cells have 46 chromosomes, each identical to those of the primary germ cell, from which they derived. By means of mitotic division, all of the primary female oocytes are produced prior to birth. There are about 2 million such germ cells.

By puberty the female supply of primary oocytes is reduced to between 10,000 and 30,000. Shortly before ovulation, the primary oocyte increases in size and begins meiotic division. In this reproductive process the pairs of chromosomes separate, one going to each daughter cell, producing secondary oocytes each having exactly 23 chromosomes (one of each pair) in the normal case. Most of the cytoplasm goes to one of the daughter cells. The other, called first polar body, degenerates.

The secondary oocyte begins the second part of the meiotic division (similar to mitotic division) but progresses only to the metaphase, the last stage before actual division. If fertilization takes place, the second division is completed with one of the daughter cells receiving most of the cytoplasm. This, together with the sperm, forms the fertilized ovum with a full 46 chromosomes — one set from each parent. The other cell, called the second polar body, degenerates.

* These three sections on offspring were developed under contract with Öko Institut Für Angewandte Okologie, Freiburg, F.R.G.

Only about 400 primary oocytes progress to the metaphase of the second meiotic division during the female lifetime. The average number of viable offspring produced per woman in developed countries is about two to four. Around age 50, the female ceases to form secondary oocytes.

MALES:

The primary germ cells of the male begin development around the 21st day of embryogenesis, as in the female. However unlike the female, the proliferation of primary germ cells through mitosis to form large numbers of spermatagonia does not begin until puberty (13 to 16 years). The spermatagonia then enlarge to form the primary spermatocytes which then undergo reduction division (meiosis) to produce secondary spermatocytes, each having exactly 23 chromosomes, one of each pair, in the normal case. Both spermatocytes survive.

In a second meiotic division four spermatids are produced, each of which develops into a mature sperm. The male continues to produce secondary spermatocytes for his entire lifetime. The process of spermatogenesis requires two or three weeks for completion; therefore, there is a constant replacement of active sperm.

GENETIC DISEASES:

In the 1972 report of the U.S. National Academy of Science on the Biological Effects of Ionizing Radiation (BEIR I), genetic diseases were classified as:

- autosomal dominant and X-linked diseases
- chromosomal and recessive diseases
- congenital anomalies; anomalies expressed later in life; constitutional and degenerative diseases (2)

The same classification was used by the United Nations Scientific Committee on the Effects of Atomic Radiation in 1977 (3). In its most recent report, BEIR III, recessive diseases and chromosomal aberrations are separate categories and the last category is called "irregularly inherited diseases." (4)

The last classification will be used here to facilitate comparison of findings.

UNSCEAR 1977:

In the section D, Genetic Effects of Radiation, of UNSCEAR's report on the effects of radiation, it is stated:

> "The Committee has reviewed the frequency estimates obtainable for different types of gene mutations and chromosome aberrations, particularly as applicable to the two germ cell stages which have been found to be of major importance. These are the spermatogonia and the oocytes, which constitute the permanent cell population in the male and female, respectively." (5)

NON-PERMANENT GENETIC MATERIAL:

The 260,000 ova developed per month in a population of 10^6 and the 300 to 500 million sperm required for each fertilization, have been discounted. Each month (28 days) about 1,064 viable conceptuses are formed in a population of 10^6, assuming European and North American experience. Using the estimate of H. B. Jones, Donner Laboratory, University of California at Berkeley, one might except 2 to 3 mutations per 10^3 germ cells per rad exposure (6), hence these 1,064 conceptuses would have about 4 to 6 mutations per rad parental exposure. The reason for the doubling is, of course, that one rad gonadal exposure to each parents results in two rad exposure damage to the fertilized ovum. Based on radiation damage to bone marrow or lymphatic tissue cells, about 6 conceptuses would die per rad parental exposure.

The mutations caused by radiation in the non-permanent genetic material in the population will become part of the permanent genetic material of the next generation.

ESTIMATING GENETIC EFFECTS:

UNSCEAR offers both a direct and indirect method of estimating damage to the permanent genetic material in a population of 10^6. (7)

The indirect method, use of a doubling dose, is the generally accepted approach, and will be used in this report. The doubling dose of radiation is that exposure which will double the frequency of a particular genetic effect in the population.

There are two difficult questions raised by this concept. This first is the tacit assumption that one radiation dose can be assumed to cause a doubling of Down's syndrome, or a variety of congenital malformations and anomalies, each having a different causal mechanism. There is no guarantee that a single such dose level exists.

The second problem is more subtle. The number of new spontaneous mutations which occur per generation is probably much smaller than the observed incidence rate of children with genetic diseases. The reason for this is the variable ability of mutants to reproduce. The genetic disease in a child may have derived from a spontaneous genetic change in a grandparent or great grandparent, rather than a parent. Moreover a doubling of the underlying incidence rate of a particular genetic mutation might require a gap of ten or twelve generations before it is observed as a doubling of cases in the population.

It is generally conceded that ionizing radiation is one of the most mutagenic agents known to human kind. In 16 years of experimentation with Drosophila, teams of scientists all over the world using a variety of chemicals managed to produce about 200 viable mutations. Working alone, Hermann J. Muller was able to produce 100 of these viable mutations in two months through irradiation with 50 kV X-ray. He also clearly showed reduced fertility, i.e., death of germ cells, resulted from irradiation of either male or female. These are dramatic visible effects of exposure to radiation, but many minute changes in the genes are recessive and their effect is not immediately apparent in a population. When this understanding of genetic damage is applied to humans, it will be apparent first, that the true genetic load, i.e., number of harmful genes carried in the permanent genetic material of a generation, is undoubtedly much larger than would appear from the number of live-born offspring with visible defects, and second, that increasing the genetic load may not have immediate dramatic results.

With the above reservations, we will examine estimates of the dose of radiation thought to cause a doubling of genetic mutations and disease in a population.

Table 28

DOUBLING DOSE FOR GENETIC EFFECTS

Study or Population	Genetic Effect	Doubling Dose
Atomic bomb survivors(8)	Untoward pregnancy outcomes; i.e. major congenital defect, stillborn or neonatal death	137 gonadal rems (69 rems to each parent) Lower limit: 18 gonadal rems (9 rems to each parent)
	Death during infancy or childhood	294 gonadal rems (147 rems to each parent)
	Sex chromosome aneuploids (i.e. an abnormal number)	504 gonadal rems (252 rems to each parent)
UNSCEAR 1977 (9)	"several different forms of genetic abnormality" in the mouse	100 gonadal rems (50 rems to each parent) (100 rems to spermatocyte)
NRPB - United Kingdom (10)	Based on UNSCEAR 1977 (#49 and #47)	100 gonadal rems (100 rems to spermatocyte)
Brewen and Preston (11)	Viable genetic translocations	6 to 33.4 gonadal rems (3 to 16.7 rems to each parent)
Gofman analysis of Atomic bomb studies (12)	Death prior to maturity due to gene or chromosomal damage	31 to 52 rem dose to father
Uchida et al. (13)	Somatic cell non-disjunction in mitotic division	16.7 rems to the cell
BEIR III (4)	Any genetic disorder	50-250 gonadal rem (25-125 to each parent)
Handbook	Any genetic disorder	12-250 rems average dose to the population (both parents)

The atomic bomb survivors, because of the high embryonic and fetal loss due to trauma, disruption of the basic social system and medical delivery system, rampant infections, and general loss of the more fragile portion of the population, do not form the best source of information on the genetic effects of ionizing radiation. (14) All studies suffer from a lack of precise information on genetic damage, since unless there is gross abnormality an individual is not suspected of having a genetic change. There are physical limits to the ability to detect point mutations. Even with modern banding techiques, the ability to connect point mutations with clinical manifestation of disease is very rudimentary. These recognition problems are compounded in the atomic bomb survivor population because of the social stigma attached to admission of being a survivor and having an abnormal child. Under-reporting is most probable.

In order to set "best estimate" limits on genetic effect estimates, we have assumed in this report that the BEIR III range is reasonable, but either extreme value might be in error by a factor of two.

In the Handbook, the assumption underlying UNSCEAR namely that only exposure to the male spermatagonia is of concern, was rejected. The decision is predicated on two observations: the probability that Down's syndrome is related to maternal exposure to ionizing radiation (15, 16), and the evidence for increased neoplasia (cancer) in children with maternal pre-conception irradiation (17). While there is a difference in rate of meiotic and mitotic division of germ cells in the male and female, it is not prudent to assume that mouse studies of gross genetic abnormalities showing low susceptibility for radiation damage in female oocytes warrants assuming that the genetic dose must be concentrated in the spermatagonia in order to cause detriment to the human child.

ESTIMATING GENETIC DISEASE INCIDENCE RATE:

In addition to the estimate of radiation doubling dose for genetic effects, it is necessary to know or make estimates of the number of such diseases already in the population. The two most widely used sources of such estimates are those published in UNSCEAR 1977 and BEIR III. These estimates have been seriously challenged by Dr. John Gofman (12); therefore his estimates, fully documented in his recent book, will also be given. The range of estimates used in the Handbook will be given in the last column.

Table 29

"SPONTANEOUS" GENETIC DISEASE RATES

Disease Classification	Current Incidence per 10^6 Live Births			
	UNSCEAR	BEIR III	Gofman	Handbook
Autosomal dominant and X-linked	10,000	10,000	10,000	10,000
Recessive:				
Homozygotes	1,100	1,100	1,100	1,100
Heterozygotes	—	—	—	64,900
Chromosomal	4,000	6,000	4,000-6,000	4,000-6,000
Irregularly inherited	90,000	90,000	90,000-450,000	90,000-450,000
Total	105,100	107,100	105,100-467,100	170,000-532,000

Many of the entries in the chart are guesses, with the greatest amount of dissent in those diseases labelled "irregularly inherited." On the genetic diseases where there is basic agreement, the effect is dramatic and usually fatal before the child reaches maturity. There are many genetic diseases with less visible effects omitted in this listing. A category was added, namely heterozygous recessives, since most lethal recessive genes have some health effect on the heterozygotes. An example of this is sickle cell which causes serious health problems when present in two genes and milder effects when present in one gene only. The estimate of the number of heterozygotes is made as follows:

> Let p = the probability of an offspring receiving a normal gene, and q = the probability an offspring receiving a recessive disease gene.

Assuming simple random mating in the population, the expected distribution for 10^6 offspring would be:

q^2 (10^6) = 1,100 recessive homozygotes
2 pq (10^6) = 64,900 heterozygotes
p^2 (10^6) = 934,000 normal

The occurrence of homozygous recessives can be used to estimate the q value, which then determines the other categories (18).

It should be noted that a doubling of the deleterious recessive gene frequency would lead to 4 times as many homozygous recessive births, since $(2q)^2 = q^2$. The number of heterozygotes would double with a doubling of recessive gene frequency.

The estimate of 90,000 "irregularly inherited" genetic diseases is based on a study of the population under 21 years of age done in British Columbia. This study fails to include any disease which has a genetic component with an onset time beyond age 21 years. (19)

In addition to the failure to include adult diseases, the BEIR I report from which both UNSCEAR 1977 and BEIR III took the estimate, made an arbitrary decision to consider only 1.5% of constitutional and degenerative diseases as genetic.

> "This figure is taken to be 1.5%, but is quite arbitrary, depending upon what diseases are included. Anemia, diabetes, schizophrenia, and epilepsy, for example, are included. Heart disease, ulcer and cancer have not been included, although there is known to be a genetic component in each." (20)

It is thought that the consequences of atherosclerosis alone (omitted from the estimate) causes 50% of the premature deaths in the United States (12). It seems reasonable therefore, to multiply this estimate of irregularly inherited diseases by a factor of 5 to allow for the omissions. Even this estimate may be much too conservative. Dr. John Gofman suggests that it may be more appropriate to multiply the number of irregularly inherited diseases by a factor of between 6 and 100 (12).

A chart will be developed, using the estimates from the UNSCEAR 1977 and the Handbook best estimate of the number of excess genetic diseases per 10^6 live births expected per generation after gonadal exposure to 1 rem ionizing radiation. It is not known what proportion would be seen in the first generation since this depends on the ability of mutants to procreate. Hence the "equilibrium" generation is assumed.

Table 30

EVENTUAL EXCESS IN GENETIC DISEASE PER GENERATION PER REM PARENTAL EXPOSURE TO IONIZING RADIATION PER 10^6 LIVE BIRTHS*

Disease Classification	**UNSCEAR 1977 (21)**	**Handbook 1982*** **
Autosomal Dominant and X-linked	100	40 - 830
Recessive:		
Homozygous	very slow increase	8.8 - 182.6
Heterozygous	—	260 - 5,387
Chromosomal Diseases	40	16 - 498
Irregularly Inherited Diseases	45**	180 - 3,735 ****
Total (approx.)	185	500 - 10,600

* Equilibrium estimate, either parent exposed.
** Assumes a 5 per cent mutational (inherited) component and 95% environmental component.
*** A doubling dose of 250 rem would imply a disease increase of 0.4% per rem dose to the population. A doubling dose of 12 rem would imply a disease increase of 8.3% per rem dose to the population.
**** Assumes a 50 per cent mutational (inherited) component and a 50 per cent environmental component.

It will be noted that this "best estimate" of 500 - 10,600 genetic diseases per generation per 10^6 live births per rem gonadal exposure compares favorably with other estimates given in the literature:

60 - 1100 BEIR III (22)

191 - more than 20,000 Gofman (23)

In the absence of firm data on the genetic component of irregularly inherited diseases, 50 per cent genetic and environmental contributions were assumed. This is consistent with a two stage theory of disease etiology. Assuming a 95% environmental component (as done in UNSCEAR 1977) places a more serious burden of illness on radiation pollution related somatic illnesses than is generally assumed. Given the persistence of radiation in the environment, this external contribution to each generation's radiation exposure history could result in even greater estimates of observable disease than are assumed in this report.

A normal European or North American population of 10^6 would have about 420,000 births per generation. Hence the actual number of genetically damaged offspring per generation per rem gonadal exposure per 10^6 persons would be (in the equilibrium case):

UNSCEAR 1977	78
BEIR III	31 to 475
Gofman (1981)	80 to more than 8,400
Handbook	210 to 4,452

EXAMPLES OF USES OF TABLES 28 TO 30

Sample Question 1: According to a State law all first year college students must undergo a physical examination including medical X-rays before admission to classes. If 5 million students of child-bearing potential received an average genetically significant dose of 0.05 rem during this examination, what effect, if any, would this have on their offspring?

Solution: It is usually assumed that any exposure to ionizing radiation will cause some genetic damage; therefore the threshold for this effect is zero. From Table 28, one notes that estimate for doubling genetic disorders is 12-250 rad. Assuming intermarriage among the 5 million:

$$100\% \div 12 \text{ rad} = 8.3\% \text{ increase per rad (or rem)}$$

$$8.3\% \text{ per rem} \times 0.05 \text{ rem} = 0.4\% \text{ increase}$$

$$100\% \div 250 \text{ rad} = 0.4\% \text{ increase per rad (or rem)}$$

$$0.4\% \text{ per rem} \times 0.05 \text{ rem} = 0.02\% \text{ increase}$$

The X-rays will be expected to increase genetic diseases in this sub-population by 0.02% to 0.40%.

If one assumes that these students eventually replace themselves, i.e., each couple averages two children, there will be 5 million offspring. Using Table 29 one notes that there are between 170,000 and 532,000 genetic diseases per 10^6 live births. The expected radiation related increase in these diseases at equilibrium is given on Table 30, and for this subgroup of 5 million births with a 0.05 rem exposure, the estimate would be:

$$(500 \times 10^{-6} \text{ per rem}) \times 5 \times 10^6 \times 0.05 \text{ rem} = 125$$

$$(10{,}600 \times 10^{-6} \text{ per rem}) \times 5 \times 10^6 \times 0.05 \text{ rem} = 2{,}650$$

The excess in genetic diseases per generation induced by this X-ray program will be expected to be between 125 and 2,650 cases.

Sample Question 2: A young girl is found to have a spinal deformity and a physician decides to do a series of spinal X-rays each year to monitor changes during the growth years. This series of X-rays gives a genetically significant dose of 1.2 rad, and is given yearly between ages 3 and 18. How does this effect the ability of the girl to bear normal children?

Solution: Women carry all the ovum they will ever have from birth. This woman was exposed to 19.2 rad to the gonads from the 16 spinal X-ray examinations. One notes in Table 28 that the doubling dose for genetic effects when only one parent is exposed would be 24 to 500 rad. The young woman might expect between:

$$19.2 \div 24 = 0.08 \text{ or } 80\% \text{ increase,}$$
$$\text{and } 19.2 \div 500 = 0.04 \text{ or } 4\% \text{ increase}$$

i.e., 4% to 80% increase in the risk of birth defects to her offspring. If her basic risk is average, she might have a 17% to 53% chance of having an infant with a genetic disease (see Table 29). Her risk is increased to 18% to 95%. If we consider only the autosomal dominant, x-linked, homozygous recessive and chromosomal disorders, which are the most severe genetic effects, her basic risk would be 1.5% to 1.7%. This might be expected to increase to 1.6% to 3.1% after the X-ray exposures.

Sample Question 3: A population of 3 million is exposed to an average dose of 0.005 rem ionizing radiation each year for the 40 year life of a nuclear facility. What would be the expected excess in genetic disease attributable to this exposure induced in that population per generation, after the disorders reach equilibrium?

Solution: About 14,000 births occur each year in a population of one million, implying 42,000 births per year for a population of three million. A "generation" is usually taken to mean 30 years, or in this case:

$$30 \times 42{,}000 = 1.26 \times 10^6 \text{ births}$$

It is assumed that there is intermarriage in the population. The genetically significant dose for each parent would be:

$$30 \text{ years} \times 0.005 \text{ rem} = 0.15 \text{ rem}$$

since the average age at childbirth is 30 years. Using Table 30 and adjusting for the number of births and dose, one obtains:

$$(500 \times 10^{-6} \text{ per rem}) \times 1.26 \times 10^6 \times 0.15 \text{ rem} = 94.5$$

$$(10{,}600 \times 10^{-6} \text{ per rem}) \times 1.26 \times 10^6 \times 0.15 \text{ rem} = 2{,}003$$

i.e., there would be between 94 and 2,003 extra genetically diseased offspring per generation.

Using Table 29, one can see that:

$$17 \times 10^4 \times 1.26 = 21.4 \times 10^4$$

$$53.2 \times 10^4 \times 1.26 = 67.0 \times 10^4$$

between 21.4×10^4 and 67.0×10^4 genetically diseased children would have been expected in this population.

The real increase in ill health lies between:

$$94.5 \div (67.0 \times 10^4) = 0.014\% \text{ and } 2{,}003 \div (21.4 \times 10^4) = 0.93\%$$

Because the nuclear facility operates for 40 years, offspring born for the first ten years of the second generation would also receive direct genetically significant doses. This source of increased ill health is not included in the estimate. Also not calculated in these examples are, of course, the reproductive loss, teratagenic effects, and direct cancer effects.

REFERENCES: Genetic Effects

1. The Developing Human: Clinically Oriented Embryology, by Keith L. Moore, W. B. Saunders Co. 1974.
2. BEIR, 1972, page 57.
3. UNSCEAR, 1977, Page 539.
4. BEIR III, 1979 page 85.
5. UNSCEAR, 1977, page 8 paragraph #40.
6. Jones, H. B., Estimate of Effect of Radiation upon Human Health and Life Span. Proceedings of the Health Physics Society, June 1956, pages 114-126.
7. UNSCEAR, 1977, page 9 paragraph #45-#49.
8. Schull, W. J. et al. "Genetic Effects of the Atomic Bombs: A Reappraisal". **Science**, Vol. 213. 11 September, 1981, pages 1220-1227.
9. UNSCEAR 1977, pages 9 paragraph #49.
10. Smith, H. and J. W. Stather. "Human Exposure to Radiation Following the Release of Radioactivity from a Reactor Accident: A Quantitative Assessment of the Biological Consequences." National Radiological Protection Board, Harwell, U.K. November 1976.
11. Brewen, J. G. and R. J. Preston. "Analysis of X-ray induced chromosomal translocations in human and marmoset spermatogonial stem cells." **Nature**, Vol. 253, 1975, pages 468-470.
12. Gofman, John W., **Radiation and Human Health,** Sierra Club Books, San Francisco, 1981.
13. Uchida, I. A., et al. "Chromosome aberrations induced in vitro by low doses of radiation: Nondisjunction in lymphocytes of young adults." **American Journal of Human Genetics**, Vol. 27, 1975, pages 419-429.
14. Stewart, A. M. "Delayed effects of A-bomb radiation: a review of recent mortality rates and risk estimates for five-year survivors." **Journal of Epidemiology and Community Health**, June, 1982, Vol. 36, No. 2, pp 80-86.
15. Uchida, I. A., et al. "Maternal Irradiation and chromosome aberrations." **Lancet**, 1968, pages 1045-1049.
16. Kochupillai, N. et al. "Down's syndrome and related abnormalities in an area of high background radiaton in coastal Kerala, **Nature**, Vol. 262, July 1, 1976, pages 60-61.
17. Shiono, P. H., et al. "Preconception Radiation, Intrauterine Diagnostic Radiation and Childhood Neoplasia." **Journal National Cancer Institute** (U.S.) Vol. 65, No. 4. October 1980, pages 681-686.
18. Chin Chun Li **Population Genetics**, the University of Chicago Press, Fourth Edition, 1963, pages 6-7.
19. Trimble,B. K. and J. H. Dougherty. "The amount of hereditary disease in human populations." **Annals of Human Genetics** (London) Vol. 38, 1974, pages 199-223.
20. BEIR I, page 56.
21. UNSCEAR 1977, page 539.
22. BEIR III, page 85.
23. Gofman, J. W., 1981, p. 849.

MORTALITY AND RESORPTION

1. Pre-Conception:

In a population of 10^6, there are about 345,000 women under 50 years of age. Women carry from birth all of the oocytes they will ever have, and about 400 of these mature to viable ova. The Handbook assumes an average of 200 viable ova are present per woman on any given day, and that there are 10^4 loci per ovum. One rem ionizing radiation would be expected to cause: $(3.45 \times 10^5) \times (2 \times 10^2) \times 10^4 \times (5 \times 10^{-7}) = 3.45 \times 10^5$ lethal mutations (1). An average of one per 200 ova, 0.5%, would be lost causing a reduction in female fertility of 0.5%. In terms of live births, this would mean a reduction of birth rate by 70 births per year over the 30 years following exposure.

The estimate of 5×10^{-7} mutations per locus per rem is based on mouse oocyte studies, which used exposure rates of 90R/minute. This is comparable to a dose rate of 1.5 rad per second, that of diagnostic X-ray (2). The BEIR I report assumes 1/20th this mutation rate, under their assumption that the dose of ionizing radiation would be chronic, i.e. delivered at a slower dose rate. This assumption of dose rate effect reduction is based on research on effects for total doses above 80 rem, usually in the 200-400 rem range. There is no evidence to support a dose rate effect below 80 rem (4). In fact, dose fractionation may actually increase mutations (5, 6). Hence Handbook estimates do not include a reduction for dose rate effect at the one rad dose level.

Radiation induced lethal mutation rates in cultured, mammalian cells vary from 1 to 18×10^{-7} per locus per rad (7). The rate appears to be comparable to that for the mouse.

2. One to five days after fertilization:

The death rate for fertilized ova varies inversely with dose in the pre-implantation stage of growth. About 195 embryos would be expected to be at this stage of gestational development at any given day in a population of 10^6. Of these embryos exposed to ionizing radiation, one would expect:

0.8 to 5.8 embryonic deaths per rem/day
1.0 to 6.6 embryonic resorptions per rem/day

1.8 to 12.4 embryonic losses per rem/day.

The higher estimate is appropriate for lower total dose.

Table 31

EVIDENCE FOR EXCESS MORTALITY RATE
IN MICE EXPOSED IN UTERO BEFORE IMPLANTATION

Author	Days Post Coitus	Dose in R	% (Excess) Mortality	Excess Mortality per R per 100
Jensh and Brent (8)	1	0	(5.3)	—
Rugh (9)	0.5	5	15	3
Jensh and Brent (8)	1	10	10.6	0.5
Rugh (10)	0.5	10	21.3	2.1
	1.5	15	0.7	0.05
Jensh and	1	20	14.1	0.4
Brent (8)	1	30	18.2	0.4
Russell and	1	150	65-70	0.4
Russell	0.5 to 2.5	200	80	0.4

Table 32

EVIDENCE FOR EXCESS RESORPTION RATE IN MICE EXPOSED IN UTERO BEFORE IMPLANTATION

Author	Days Post Coitus	Dose in R	% Excess Resorption	Resorption per R per 100
Rugh (10)	0.5	5	14.3	2.9
Ohzu (12)	0.5	5	21.5	4.3
	1.5	5	14.8	3.0
Rugh (10)	0.5	15	19.0	1.3
	1.5	15	9.0	0.6
Ohzu (12)	0.5	15	27.6	1.8
	0.5	25	35.5	1.4
	1.5	15	20.5	1.4
	1.5	25	21.9	0.9
Rugh (9)	0.5	50	42.0	0.8
	1.5	50	5.0	0.1
	2.5	50	24.0	0.5

The following estimates were adopted for use in the Handbook:

Total dose to pre-implantation ovum	% Excess Mortality per rem	% Excess Resorption per rem	Total Embryonic Loss per rem
<10 rem	3.0	3.4	6.4
10 - 50 rem	0.7	1.2	1.9
>50 rem	0.4	0.5	0.9
Range	0.4 to 3.0	0.5 to 3.4	0.9 to 6.4

Assuming a fertilized ovum pre-implantation loss between 0.9 and 6.4 per hundred per rem is equivalent to assuming the 100% lethal dose for pre-implantation ovum to be between 16 and 111 rem. This is consistent with observations of mouse ova which show significant delay in first cleavage, cell vacuolization, giant cells with extra chromosomes, uneven cell growth, dissociation of cells and disintegration of embryos at doses as low as 15R (9).

The reader may note that at doses above 200 rem some 20 to 30% of the ova survive implantation. However, their survival to live birth has not been documented, nor is it known whether or not this fraction was designated as lost through resorption or after birth and therefore not called an embryonic death.

3. Six to ten days after fertilization:

During implantation the embryo is again at risk of death or resorption. Of the 195 embryos expected to be in this gestational stage daily, one would expect:

0.4 to 0.6	embryonic deaths/rem/day
0.4	embryonic resorption/rem/day
0.8 to 1.0	embryonic losses/rem/day

Table 33

EVIDENCE FOR MORTALITY RATE IN MICE EXPOSED DURING IMPLANTATION

Author	Days Past Coitus	Dose in R	% Mortality	Excess Deaths per R per 100
Russell and Russell (11)	3.5	200	69	0.3
Phemister	3	250	61	0.2
et al (13)	4 - 5	250	67	0.3
Handbook	—	—	—	0.2 to 0.3

Table 34

EVIDENCE FOR RESORPTION RATE IN MICE EXPOSED DURING IMPLANTATION

Author	Days Post Coitus	Dose in R	% Resorption % Resorption	Excess Resorption per R per 100
Rugh (10)	3.5	50	9	0.2
	4.5	50	8	0.2
Average	—	—	—	0.2

A resorption rate of 0.2 per R per 100 represents an embryonic loss between 0.4% and 0.5% per rem per day during implantation.

4. Day eleven to eighty-four after fertilization:

About 2,886 post implantation embryos would be expected in a population of 10^6. An exposure of one rem would be expected to result in:

4.6 - 4.9 embryonic deaths/rem/day
5.5 - 7.2 resorptions rem/day
10.1 - 12.1 embryonic losses/rem/day

Table 35

EVIDENCE FOR EXCESS MORTALITY IN MICE EXPOSED AFTER IMPLANTATION

Author	Days Post Coitus	Dose in R	% Excess Mortality	Excess Mortality per R per 100
Phemister	8.0	150	18	0.20
et al (14)	15.0	150	24	0.16
	18.0	150	29 -48	0.19 - 0.32
	21.0	150	23	0.15
	28.0	150	26	0.17
Phemister	8	250	59	0.24
et al (13)	9 - 10	250	48	0.19
	12 - 14	250	23	0.09
	15	250	28	0.11
Average	—	—	—	0.16 - 0.17

Table 36

EVIDENCE FOR EXCESS RESORPTIONS IN MICE EXPOSED AFTER IMPLANTATION

Author	Days Post Coitus	Dose in R	% Excess Resorption	Excess Resorption per rem per 100
Jacobson (15)	7.5	0	(10.4 summer)	—
			(10.0 winter)	—
	7.5	5	- summer	—
			2.6 winter	0.52
	7.5	20	1.5 summer	0.08
			5.7 winter	0.28
Rugh (9)	5.5	50	17.5	0.34
	6.5	50	8.0	0.16
	7.5	50	—	—
	8.5	50	—	—
	9.5	50	10.0	0.20
Jacobson (15)	7.5	100	22.8 summer	0.23
	7.5	100	33.0	0.33
Rugh (9)	8.5	200	19.6 virgins	0.10
			50.0 old breeders	0.25
Average	—	—	—	0.19 to 0.25*

* Averages were calculated with and without the zero response categories.

5. Later mortality:

Exposure to 110-150 rem in utero has been shown to cause a significant increase in post-partum infant mortality (16), and 300 rem has been shown to cause 100% fetal or neonatal mortality (17). Hence, 0.33% fetal or infant death rate per rem exposure is a reasonable estimate of reproduction loss in the population for day 85 to 252 fetuses. There would be 6,513 fetuses of this gestational age, resulting in 21.5 deaths (either fetal or infant) per rem exposure in a population of 10^6.

6. Fertility of offspring exposed in utero:

Fertility reduction has been noted after exposure in utero. Oocyte number is reduced after exposures at or above 25R and the ovarian, pituitary and adrenal weight are reduced (18). Significant reduction of reproductive potential in males exposed in utero has been noted at or above 100R (19).

7. Fertility of future generations:

Reduced fertility in future generations has been demonstrated in both irradiated and non-irradiated progeny of an irradiated male. In one experiment, one population of male mice of each generation were exposed to 3.7 rad acute irradiation and in another population, male mice of each generation were exposed to 3.9 rad chronic irradiation. Their progeny were compared with a non-irradiated control population of mice. All the mice originated from the same strain of mice, and all were sibling mated. They received good care in a laboratory setting; hence their survival might be presumed to be better than might occur in the wild.

At the end of 6 generations there were only 15% of the expected number of offspring in the sample in which males of each generation received an acute dose of 3.7 rad, and only 47% of the expected number of offspring in the sample in which males received a chronic dose of 3.9 rad. The expected numbers were based on the observed control population. This difference in infertility might indicate a slow dose rate effect of 3, i.e., it would require about 12 rad chronic dose to produce the same fertility reduction as would be produced by an acute dose of 4 rad. The final test generation of mice was exposed to no radiation; however the offspring of the irradiated series continued to have a significantly higher pre-implantation reproductive loss relative to the controls (20). There is no indication that selection produced either a more fertile or a radiation resistent offspring.

Human Data:

There is evidence of higher mortality rate of offspring prior to age 1 year in women exposed to ordinary diagnostic irradiation. In an epidemiological survey of three million leukemic and non-leukemic children, ages 1 to 15 years, sampled over a three year period, a deficit of children in the 1-4 year age group with maternal pre-conception or in-utero X-ray was noted.

In the random sample of 223 children age 1-4 years, there were 85 with no maternal pre-conception or in-utero irradiation. These children were used to estimate the expected proportion of children in each of four pathological categories:

(1) No viral indicator diseases and no maternal history of miscarriages and stillbirths.

(2) Childhood virus diagnosed one year or more prior to interview.

(3) Maternal history of miscarriages or stillbirths prior to this conception.

(4) Both pathological factors, viral disease and maternal reproductive problems, present.

It is reasonable to assume that the proportion of children in each of these pathological categories would be the same whether there was a history of maternal pre-conception or in-utero irradiation or not. This asumption was acceptable when tested with a chi-square test (Chi-square with 6 degrees of freedom was 3.6). In the same random sample of control children, there were four radiological categories:

(1) no irradiation

(2) maternal preconception irradiation

(3) in utero irradiation

(4) both maternal preconception and in utero irradiation.

The assumption was made that the 128 child controls with no pathological factor would have the same proportion in each radiation exposure category as the children with some pathological factor. This assumption also provided acceptable by chi-square criterion (Chi-square with 6 degrees of freedom was 7.6).

Using the non-irradiated children to estimate the proportion and number expected in each pathological category, and the children with no pathological problem to estimate the proportion and number expected in each radiological category a table of expected numbers of children in the various pathological/radiological categories could be constructed.

In **every** category, the observed number of children, age 1-4 years, was less than the expected number of children.

The total number of children age 1-4 years, among those with maternal pre-conception or in utero radiation exposure was only 79% of the number expected on the basis of non-exposed children. The probability of this finding being due to chance is less than 0.002. It is therefore not a random happening, and it can be assumed that the probability of survival to age one is significantly reduced with maternal pre-conception or in utero exposure to ionizing radiation (21). It is impossible to quantify the reproductive loss per rem exposure using this data since maternal medical X-ray exposure was not measured. However, there seems little doubt that humans, like other mammals, suffer reproductive losses when exposed to ionizing radiation levels even slightly above backgound.

Table 37

SUMMARY ESTIMATE OF GENETIC LOSS THROUGH MORTALITY OR RESORPTION AFTER EXPOSURE TO IONIZING RADIATION

	Developmental Stage	**Loss per 10^2 per rem**	**Loss per rem in a population of 10^6**
1.	Pre-conception loss in the population	0.5	2100 over a 30 year reproductive lifetime
2.	Post-fertilization but pre-implantation embryos	0.9 to 6.4	1.8 to 12.4 per day
3.	Implantation period	0.4 to 0.5	0.8 to 1.0 per day
4.	Organogenesis period	0.35 to 0.42	10.1 to 12.1 per day
5.	Fetal period	0.33	21.5 per day
6.	Offspring of those exposed in utero	unknown	unknown
7.	Future generations	unknown	unknown
	Total:		
	Unfertilized	0.5	2100
	Fertilized	0.3 - 0.5	34.2 - 47.0 per day

Since UNSCEAR 1977 and BEIR III did not judge this genetic loss to be of concern to the population, there are no estimates with which to compare.

EXAMPLES OF USES OF TABLE 37

Sample Question 1: In a nuclear accident a population of 2.7 million was exposed to an average dose of 5 rem ionizing radiation. The dose was essentially received over a 3 day period, with 3 rem on the 1st day, 1.5 rem on the second day and 0.5 rem on the third day. What would be the expected genetic loss in the population attributable to the exposure?

Solution: Using Table 37, and adjusting for a population of 2.7 million and an exposure of 5 rem, one obtains:

Unfertilized loss:

$$(2{,}100 \times 10^{-6} \text{ per rem}) \times 2.7 \times 10^{6} \times 5 \text{ rem} = 28{,}350$$ over a 30 year reproductive lifetime.

Fertilized loss:

$$(34.2 \times 10^{-6} \text{ per rem}) \times 2.7 \times 10^{6} \times 5 \text{ rem} = 462$$
$$(47.0 \times 10^{-6} \text{ per rem}) \times 2.7 \times 10^{6} \times 5 \text{ rem} = 634$$

Between 462 and 634 embro or fetuses would be resorbed or aborted.

Sample Question 2: A woman who is about one month pregnant is in an automobile acident. The hospital Emergency Room physician ordered a series of X-rays, which gave an estimated 10 rad dose to the fetus. Tha woman aborted the fetus three days later. What is the probability that the X-ray exposure induced the abortion?

Solution: Obviously the accident, tension and possible medications may have contributed to the abortion. Using Table 37, one can calculate the loss per 10^2 embryos in the organogenesis period (days 17 to 43 after conception) and adjusting to the 10 rad (rem) dose to the embryo:

$$(0.35 \times 10^{-2} \text{ per rem}) \times 10 \text{ rem} = 3.5 \times 10^{-2}$$
$$(0.42 \times 10^{-2} \text{ per rem}) \times 10 \text{ rem} = 4.2 \times 10^{-2}$$

The chances that the abortion was due to the X-ray are 3.5 to 4.2 in a hundred.

REFERENCES: Mortality and Resorption

1. The estimate of radiation induced mutations used is 5 x 10^{-7} per locus per rad, as suggested by: "Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review", by D. A. Hoffan, R.P. Felton, and W.H. Cyr, Division of Biological Effects, U.S. Department of Health and Human Services, HHS Publication FDA 81-8170, August 1981.
2. Searle, A. G., "Mutation induction in mice," **Advances in Radiation Biology** 4:131-207 (1974).
3. BEIR I, page 52 (1972).
4. W. L. Russell and L. B. Russell, "Radiation Induced Genetic Damage in Mice." Progress in Nuclear Energy Series VI. **Biological Sciences** 2, p. 179 (Pergamon Press, INC., New York, 1959).
5. W. L. Russell, Proceedings National Academy of Science, 48: 1724 (1962).
6. H. J. Muller. "Damage from point mutations in relation to radiation dose and biological conditions," In: **Effect of Radiation on Human Heredity**, page 25 (World Health Organization, Geneva 1957).
7. U.S. Health and Human Services Publication FDA 81-8170, August 1981, page 51.
8. Jensh, R. P. and R. L. Brent, "Radiation hazards on the first day of life." **Teratology** 5: 258 (1972).
9. Rugh, R., "Major radiobiological concepts and effects of ionizing radiation on the embryo and fetus." In: **Response of the Nervous System to Ionizing Radiation,** Editors T. Haley and Snider, pp. 3-26 (1962).
10. Rugh, R., "Low levels of X irradiation and the early mammalian embryo." **American Journal Roentgenology** 87:559-566 (1962).
11. Russell, L. B. and W. L. Russell, "An analysis of the changing radiation response of the developing mouse embryo." **Journal Cell Comparative Physiology** 43: 103-149 (1954).
12. Ohzu, E. "Effects of low dose X irradiation on the early mouse embryo." **Radiation Research** 26: 107-113 (1965).
13. Phemister, R. D. et al. "Irradiation of the canine conceptus: Tetratogenic, lethal and growth retarding effects." In: **Laboratory Animals in Drug Testing**, Editor A. Spiegel, pages 311-323 (1973).
14. Phemister, R. D. et al. "Radiosensitivity of the developing beagle." **Radiation Biology of the Fetal and Juvenile Mammal.** Editors: M.R. Sikov and D.D. Mahlum, pp. 395-406 (1969).
15. Jacobson, L. "Low dose X irradiation and teratogenesis: A quantitative experimental study with reference to seasonal influence on dose effects." Dissertation, University of Copenhagen Copenhagen (1968).
16. Murphree, R. L. and H. B. Pace, "The effect of prenatal radiation on post natal development in rats." **Radiation Research** 12: 495-504 (1960).
17. Russell, L. B. et al. "Comparison of the effects of acute, continous, and fractionated irradiation during the embryonic development." In: **Immediate Low Level Effects of Ionizing Radiation.** Editor: A.A. Buzzati-Traverso. Pages 343-358 (1960).
18. Beaumont, H. M. "Effect of irradiation during fetal life on the subsequent structure and secretory activity of the glands." **Journal of Endocrinology** 24: 325-339 (1962).
19. Rugh, R. and M. Wohlfrom. "Can X irradiation prior to sexual maturity affect the fertility of the male mammal (mouse)?" **Atompraxis** 10:33-41 (1964).
20. D. J. Mewissen, A. S. Ugarte. "Cumulative Effects from Exposure of Male Mice to Tritium for Ten Generations." International Atomic Energy Agency Symposium, Vienna. Biological Implications of Radionuclides Released from Nuclear Industries. Vol. 1, page 215. IAEA — SM 237/67 (1979).
21. R. Bertell. "Radiation Exposure and Human Species Survival." **Environmental Health Review**. Vol. 25, No. 2 (1981).

CONGENITAL (TERATAGENIC) EFFECTS

Radiation health damage to a population is usually considered under two categories: somatic, if it effects the person exposed, and genetic, if it effects the future offspring of the person exposed. The exposure of an unborn embryo or fetus is not included in either category. The exposure of the pregnant woman includes the direct exposure of an already conceived offspring, even though the offspring is not yet born. The effects of such exposure are called congenital or teratogenic. Abnormalities which result are usually referred to as congenital malformations or congenital anomalies.

Irradiation to offspring in utero (in the uterus) can result in what are called stochastic or non-stochastic health effects. Stochastic are "all or none" events; for example, the child either develops cancer during childhood or does not develop cancer during childhood. The non-stochastic events are a matter of degree of severity, rather than "all or none" effects. For example, the degree of mental and/or physical retardation caused by the exposure to radiation may vary from slight to severe.

The type of damage done to a developing embryo or fetus is related to the particular stage of development at the moment of irradiation. If the brain and central nervous system are just beginning to evolve from one or two primitive cells and these cells are damaged, then the entire brain and central nervous system will be "built" with the damaged cells. The remainder of the embryonic cells, including the primitive germ cells may remain undamaged. In this case, the offspring might be retarded, deaf or blind, yet that would not effect any future children that this disabled person conceives. Congenital defects may or may not be inheritable, depending on the embryonic stage of development at the time of exposure and whether or not the embryonic or fetal germ cells developed from, or were part of, the damaged cell lines.

Most projections of health effects for radiological accidents consider only damage to the already constituted population (those already born) or to their primary spermatocytes/oocytes (called the permanent genetic material of the already constituted population) as "of concern". They do not deal with damage to secondary spermatocytes/oocytes or teratogenic damage, even though this can cause great human suffering nor do they deal with damage to the primary spermatocytes/oocytes of the population in utero at the time of a radiological accident.

The Table 38 shows the general periods of development for the embryo and fetus, together with the expected number of conceptuses at each stage of development in any one day, in a population of 10^6 with about 14,000 births per year.

Table 38

EXPECTED NUMBER OF CONCEPTUSES AT EACH DEVELOPMENT STAGE ON ANY GIVEN DAY IN A POPULATION OF 10^6*

Stage	Human age (days)	Developmental activity, probable susceptible tissue	Number in a population of 10^6
	1	Fertilization	234
	2	Cleavage: 1 to 4 cells	
Pre-Implantation	3	Cleavage: 5 to 8 cells	
	4	Norula	
	5-6	Blastula	
Implantation	7-9	Early implantation	234
	10-12	Continued implantation, primitive streak	
Organo-genesis (Embryo)	13-16	Earliest neurogenesis	156
	**17-20	Neurogenesis; head; eye; thyroid and heart primordia; beginning of umbilical cord.	156
	**21-25	Anterior neuropore: primitive germ cells and hemopoiesis in yolk sac; heart; vitelline vessels, aortic arches; oral membrane, otic invagination; gut, liver;	195
	**25-29	Active organogenesis; all primary brain parts; myocardial pulsations and circulating blood; all sense organs and optic lens; lung primordia; posterior limb buds; mesonephric tubules	195
	**30-34	Early preskeletal chrondrification; pharyngeal pouches; pancreas; spinal nerves; sympathetic system; semi-circular canals; posterior limb buds; bronchi, migrating germ cells; corpus callosum	195
	**35-39	Differentiation of appendages and sense organs; brain; reflex pathways	195
	**40-43	Early fetus; basic organogeny completing; atrioventricular valve; primary lid folds	156
	44-50	Chondrification of ribs; muscles of esophagus epithelial cords of testis; enucleate erthrocytes	273
	51-65	Cartilage in humerous; gonad differentiation	585
	66-105	Cerebellum fused at midline; corpus callosum alveoli; gastric glands; ossification of centrum	1,560
Fetus	106-252	Growth	5,733
		SUM	9,867

* Adapted from Rugh R.: Chap, 5, Medical Radiation Biology, p. 85, Ed. Gaulden, M. E., Darylingle, etc., W. B. Saunders Co., Philadelphia, 1973.

** Period of maximum radiosensitivity in the mouse, probably the same in the human.

CONGENITAL MALFORMATIONS

The table lists all of the congenital anomalies reportedly caused by human fetal X-irradiation. All have been experimentally produced in mouse or rat when they could be recognized and analyzed (1). The obvious exceptions to experimental verification are mental deficiency, Mongolism (Down's Syndrome) and idiocy. However, learning disorders in mice and rats after in-utero X-irradiation have been well documented.

CONGENITAL ANOMALIES REPORTED FOLLOWING HUMAN EMBRYONIC AND FETAL X-IRRADIATION

1. Microcephaly (most frequent)
2. Hydrocephalus
3. Porencephaly
4. Mental Deficiency
5. Mongolism
6. Idiocy
7. Head ossification defects
8. Skull malformations
9. Micromelia
10. Microphthalmus
11. Microcornea
12. Coloboma
13. Strabismus
14. Cataract
15. Chorioretinitis
16. Nystagmus
17. Stillbirth increase
18. Live birth weight decrease
19. Neonatal and infant death increase
20. Ear abnormalities
21. Spina bifida
22. Cleft palate
23. Deformed arms
24. Clubfeet
25. Hypophalangism
26. Syndactyly
27. Hypermetropia
28. Amelogenesis
29. Odonotogenesis imperfecta
30. Genital deformities

The type and rate of malformations vary with the stage of embryonic development at the time of exposure. The following chart is based on animal studies, and represents a first attempt to estimate the magnitude of embryonic damage.

Table 39

HUMAN EXPECTED RATE OF CONGENITAL ANOMALIES BY GESTATION DAY, EXTRAPOLATED FROM ANIMAL STUDIES

Day	Rate per rem	Type	Number expected in a population of 10^6
1	Significant increase	Polydactyly (<5 rem) (2)	—
	Significant increase	Cataracts (>100 rem) (3)	—
2-6	1.0 per 10^3	Excencephaly (4, 5)	0.195
6-10	0.6 per 10^3	General (6)	0.117
8-10	Significantly slower	Locomotive Performance (5-10 rem) (7)	—
11-16	0.15 per 10^3	General (6, 8)	0.035
16-18	4.0 per 10^3	Eye lesions (9)	0.468
17-43*	4.0-5.0 per 10^3	Cleft palate, skull and skeletal (day 17-40) (10, 11) Central Nervous System (12, 13, 14)	4.21 - 5.26
44-84	1.45 per 10^3	General (6)	2.32
		Total	7.35 - 8.40 per rem per day

Gestational days 17 to 43 have the highest risk of radiation related congenital malformations. On any given day 1053 embryos would be expected to be in this critical stage of organogenesis.

A second approach to estimating the per rem congenital malformation rate, using Russell's estimate of 100% malformation dose seems to confirm the general consistency of this estimate. This generally strengthens confidence that the error probability for these estimates is reasonably small.

It has been reported by Russell (15, 16) that a 200 rem dose to an embryo during organogenesis has a 100% probability of producing some type of malformation. Assuming a general rate of 0.5% malformation per rem exposure for the human embryonic days 15-35, one would predict 4 congenital malformations per rem per day in a normally distributed population of 10^6. This is reasonably consistent with the estimate used here, assuming that the remaining 63 days of embryonic development have a lower rate of malformation, approximately 0.14 to 0.18% congenital malformations per rem exposure.

During the fetal period, days 85 to 252 (or birth), radiation exposure continues to be associated with an increase in mortality, infertility, lower birthweight, lower postnatal weight gain, lower organ weight (pituitary and adrenals), malformations, central nervous system anomalies, tumors, biochemical disorders, motor function and learning disorders, and eye damage. Developmental abnormalities observed after fetal irradiation are, however, more rare than those observed after exposure in the first trimester.

Human studies of fetal exposure to therapeutic irradiation during second and third trimester include observations of microcephaly, growth retardation (17) and Down's syndrome (18, 19). Some exposed fetuses had no observed abnormality.

It is difficult to quantify these second and third trimester effects since studies in which the effects have been observed have only imprecise measurement of the radiation exposure. In 1976, Stewart and Kneale reported that exposure to radiation in the first trimester was 16 times more likely to cause a childhood cancer than was exposure in the second or third trimester (20, 31). Under the assumption that the 16:1 ratio of radiosensitivity holds also for other congenital malformations one can calculate:

> % congenital malformations per rem exposure in the first trimester (per day):
>
> 7.35 to 8.40 per 3276 embryos, or 0.22 to 0.26%
>
> % congenital malformations per rem exposure in the second and third trimester (per day):
>
> 0.9 to 1.0 per 6,552 fetuses, or 0.014 to 0.016%.

The sum of these estimates is used in the Handbook, Table 38. These identified congenital malformations are of a serious nature, evident within the first week post partum. There will be less severe effects and also effects not detectable until later in the life of the individual. As was admitted in UNSCEAR 1977, these "minor deleterious effects, by their large number, might impose a greater total genetic (and teratogenic) burden on the population than from a smaller number of relatively more serious conditions (22)."

These proposed estimates of congenital malformation appear very conservative when compared with other estimates such as those by Dr. John Gofman (23). Based on findings at Hiroshima and Nagasaki (24), Gofman calculated the mental retardation rate per rad exposure to be between 9.8% and 28.5%. This was for **severe** mental retardation, which includes inabilty to carry on a simple conversation or care for oneself, being completely unmanageable and having to be institutionalized. Atomic bomb survivor studies did not estimate the rate of milder forms of mental retardation. As was admitted by the atomic bomb survivor researchers (24), there was a continuous array of smaller head size among survivors exposed in utero. The cut-off between "normal" and "abnormal" was arbitrary.

> "The main stimulus to skull growth is brain growth. Radiation apparently causes general cell depletion of the developing brain, with secondary small head circumference. When depletion is great enough, mental retardation ensues. With less depletion, intelligence is within normal range, but may be reduced as compared with the child's full potential had he/she not been irradiated. It seems, therefore, that even small intrauterine exposures may deprive the individual of some intelligence. (24)"

Animal studies show brain damage at radiation doses as low as 10 rad (25).

CHILDHOOD MALIGNANCIES

Several major epidemiological surveys have indicated an increased relative risk of leukemia and other childhood cancers with X-irradiation in utero.

Table 40

RESEARCH RELATING CANCER WITH IN-UTERO EXPOSURE TO X-RAY

Study	Length of Follow-up	Rel. risk of leukemia	Rel. risk of all neoplasms
MacMahon (26)	0-13 years	1.54	1.42
Diamond (27)	2-20 years	2.91*	1.49*
Bithell and Stewart (28)	Retrospective 1953-67	1.37**	1.5
Graham et al.(29)	Retrospective 1959-62	1.36	—
Ager et al. (30)	Retrospective 1953-57	1.08	—
Ford et al. (31)	Retrospective 1951-55	1.47	—
Kaplan (32)	Retrospective 1955-56	1.39	—
Polhemus and Koch (33)	Retrospective 1950-57	1.24	—
Handbook		1.5	1.5

* only white population included
** includes lymphomas

Using the Kneale and Stewart estimate that exposure to X-irradiation (averaging 0.5 rem) in the first trimester is 16x as likely to induce childhood cancer as is exposure in the second or third trimester, in any one day in a population of 10^6, there would be about 10,000 developing embryos and fetuses. About 1.6 "spontaneous" childhood neoplasms would be expected to occur in these children, based on the U.S. rate between 1950 and 1969. Based on the relative risk of leukemia as 1.5 per 0.5 rem, in utero irradiation of these embryos and fetuses would cause an additional 0.8 cancers. This may reach an excess cancer induction rate as high as 1.6 children in an irradiated population averaging 1 rem exposure. The rate of induction per rem in utero exposure would be:

$$(1/3 \times 10^4 \times 16r) + (2/3 \times 10^4 \times r) = 0.8 \text{ to } 1.6$$

$$6r = (0.8 \text{ to } 1.6) \times 10^{-4}$$

$$r = (0.13 \text{ to } 0.3) \times 10^{-4}$$

$$16r = (2.1 \text{ to } 4.3) \times 10^{-4}$$

where r stands for the rate per 10^4 developing fetuses and 16r the rate for developing embryos.

The Handbook uses (0.13 to 0.3) x 10^{-4} as the cancer induction rate for the second and third trimester, and (2.1 to 4.3) x 10^{-4} as the cancer induction rate for the first trimester per rem exposure to x-irradiation.

Bross estimates that in utero exposure to 0.5 rem x-irradiation results in 1% of the fetuses being damaged or "affected" (34). The affected subgroup has higher susceptibility to various diseases such as asthma, urticaria, pneumonia, dysentery and rheumatic fever more than a year prior to leukemia diagnosis, and 25 times the expected rate of leukemia. Using the Bross methodology, one could posit that 2% of the embryos and fetuses exposed to 1 rem x-irradiation, or about 200 per rem per day in a population of 10^5, would be affected. Leukemia rate for U.S. children, 1950 - 1968, was 7.7 per 10^5, therefore:

$$(7.7 \times 10^{-5} \times 9{,}800) + (192.5 \times 10^{-5} \times 200) = 0.75 + 0.38 = 1.13.$$

1.13 leukemias would be expected after exposure, an increase of 0.36 over the 0.77 expected. Bross does not distinguish between trimester of exposure for measurable health effects. Given that leukemias are about 40% of all childhood cancers, and assuming that the increase in all childhood cancers is proportional to the increase in leukemia, Bross's methodoly would posit: $0.36 \div 0.4 = 0.9$ additional childhood cancers. The Bross estimate also postulates about 200 affected children who do not go on to develop leukemia.

Table 41

EXCESS CHILDHOOD NEOPLASMS PER REM EXPOSURE IN UTERO OF ABOUT 10,000 FETUSES

Study	Excess Leukemia	All Excess Neoplasms
Bithell and Stewart (28)	—	0.8 - 1.6
Bross and Natarajan (35)	0.36	0.9
Handbook	0.36	0.8 - 1.6

It should be noted that in applying Stewart/Kneale and Bross findings, a dose to the conceptus of 0.5 rem was used. Pre-conception irradiation was from routine medical diagnostic irradiation. The average annual genetically significant dose attributed to this source in the U.S is 0.075 rem. The number was doubled because of maternal exposure to pelvimetry. The assumed dose to the conceptus was normally due to a medical procedure related to the pregnancy, i.e., a pelvic examination. This average dose estimate may be too high given a great variation in doses reported, causing an underestimation of in utero cancers by a factor of three. The Handbook estimate may be considered a "best estimate" at this time.

LOWER BIRTH WEIGHT

Human embryos irradiated between day 17 and day 60 experience reduced birth weight at a rate of about 0.0012% per rem(36, 37, 38). This would affect 1,716 embryos on any given day. Full term infants with reduced birth weight (below 2,500 gm.) are at a higher mortality risk than babies with birth weight above 2,500 gm.

GROWTH RETARDATION

Persisting retardation in growth throughout childhood is expected to be experienced by children exposed during day 20 to day 36 gestational development (39). About 663 children would be affected in a population of 10^6 with 10^4 developing embryos or fetuses.

Table 42

EXPECTED GROWTH RETARDATION PER REM PER DAY

Day	Rate Growth Retardation	Number Expected
20 - 24	.1 to .4% per rem	195
25 - 28	.2% per rem	156
29 - 30	.14% per rem	78
31 - 36	.03% per rem	234
	Total:	663

Atomic bomb survivors exposed in-utero exhibited growth retardation even at age 17 years. This was manifested in lower average height and weight, diminished head size and impairment in mental development (40).

Growth retardation includes both physical and mental capacity. There are volumes of supportive evidence for this effect in animals (41), as well as the observations on humans directly exposed during the growth period to man-made irradiation (42,43) and natural background radiation.

Table 43

SUMMARY OF DELETERIOUS EFFECTS OF PRE-CONCEPTION AND IN-UTERO IRRADIATION PER REM IN A POPULATION OF 10^6 IN WHICH THERE ARE ABOUT 10,000 DEVELOPING EMBRYOS AND FETUSES

Health Effect	Excess per day per rem	
	Non-Stochastic	Stochastic
1. Pre-Conception:		
Mortality (pre-conception to one year post natal)	—	May be as high as 2,100 (46)
Mild Mutations	1,876	—
2. Congenital Malformation	—	8.25 - 9.40
3. Childhood Malignancies	—	0.8 - 1.6
Mild Mutations	200*	—
4. Lower Birth Weight	1,716	—
5. Growth Retardation	663*	—
Totals	3,592	Up to 2,100 death or resorptions 9.0 - 11.0 other effects

* Probably included among those with lower birth weight.

EXAMPLES OF USES OF TABLE 43

Sample Question 1: Working women who are pregnant are sometimes allowed to receive up to 0.5 rem penetrating gamma radiation, one-tenth of the 5 rem permissible level for other radiation workers. If 25,000 pregnant women received the 0.5 rem dose at sometime during pregnancy, how many severe or mild birth defects would this induce?

Solution: Using Table 43 one obtains:

(1) $(3{,}592 \times 10^{-4}$ per rem) x 2.5 x 10^4 x 0.5 rem = 4,490
Non-stochastic effects (presumed mild);

(2) $(2{,}100 \times 10^{-4}$ per rem) x 2.5 x 10^4 x 0.5 rem = 2,625
Up to 2,625 deaths prior to age 1 year (most would be early embryonic losses);

(3) $(9.0 \times 10^{-4}$ per rem) x 2.5 x 10^4 x 0.5 rem = 11
$(11.0 \times 10^{-4}$ per rem) x 2.5 x 10^4 x 0.5 rem = 14
11 to 14 stochastic effects (cancers and serious congenital malformations).

REFERENCES

1. From Rugh, R. "Radiology and the Human Embryo and Fetus." In: **Medical Radiation Biology,** Edited by Dalrymple et al. W. B. Saunders Co., Philadelphia (1973).
2. Ohzu, E. "Effects of low dose X-irradiation on the early mouse embryo." **Radiation Research** 26: 107-113 (1965).
3. Rugh, R. et al. "Cataract development after embryonic and fetal irradiation." **Radiation Research** 22: 519-534 (1964).
4. Rugh, R. "Major Radiobiological concepts and effects of ionizing radiation on the embryo and fetus." In: **Response of the Nervous System to Ionizing Radiation,** Edited by Haley and Snider. pp. 3-26 (1962). Estimated 0.6 exencephaly per 10^3 per rad at 50 rad total exposure.
5. Rugh, R. "Low levels of X-irradiation and the early mammalian embryo." **American Journal of Roentgenology** 87: 559-566 (1962). Estimated 1.5 exencephaly per 10^3 per rad at 15 rad total exposure.
6. Phemister, R. D. et al. "Radiosensitivity of the developing beagle." In: **Radiation Biology of the Fetal and Juvenile Mammal.** Edited by M. R. Sikov and D. D. Mahlum, pp. 395-406 (1969). Estimated 0.6 malformations per 10^3 per rad during implantation.
7. Werboff, J. et al. "Behavioral effects of small doses of acute X-irradiation administered prenatally." **Atompraxis**: Vol. 9, pp. 103-105 (1963).
8. Phemister, R. D. et al. "Irradiation of the canine conceptus: Teratogenic, lethal and growth retarding effects." In: **Laboratory Animals in Drug Testing.** Edited by Spiegel. pp. 311-323 (1973).
9. Lee, A. C. and R. D. Phemister. "Ocular lesions in beagles exposed to gamma radiation at various ages." In: Annual Report for 1975, Collaborative Radiological Health Laboratory pp. 22-27. DHEW Publication No. (FDA) 76-8056 (1976).
10. Tujiki, Y. and N. Takeda. "Studies on the genesis of cleft palate in mice due to X-ray irradiation." Proceedings of Congenital Anomaly Research Association (Japan) pp. 17-18 (1961-1962).
11. Jacobsen, L. "Low dose X-irradiation and teratogenesis: A quantitative experimental study with reference to seasonal influence and dose effects." Dissertation, University of Copenhagen, Copenhagen (1968).
12. Rugh, R. and E. Grupp. "X-irradiation exencephaly." **American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine** 81: 1026-1052 (1959).
13. Ershoff, B. H. "Effects of prenatal X-irradiation on testicular function and morphology in the rat." **American Journal of Physiology** 196: 896-898 (1959).
14. Lipton, J. M. "Locomotor behavior and neuromorphologic anomalies in prenatally and postnatally irradiated rats." **Radiation Research** 28: 822-829 (1966).
15. Russell, L. B. "X-ray induced developmental abnormalities in the mouse and their use in the analysis of embryological patterns." **Journal of Experimental Zoology**. Vol. 114: 545-602 (1950).
16. Russell, L. B. and W. L. Russell. "An analysis of the changing radiaton response of the developing mouse embryo." **Journal of Cellular Comparative Physiology** 43: 103-149 (1954).
17. Dekaban, A. M. "Abnormalities in children exposed to X-irradiation during various stages of gestation: Tentative timetable of radiation injury to the human fetus, Part I" **Journal of Nuclear Medicine**. Vol. 22: 322-331 (1929).
18. Uchida, I. A. and E. J. Curtis. "A possible association between maternal radiation and mongolism (Down's syndrome). **Lancet** 2: 848-850 (1961).
19. Sigler, A. et al. "Radiation exposure of parents of children with mongolism (Down's syndrome), Bulletin John Hopkins Hospital 117: 374-399 (1965).
20. Kneale, G. W. and A. M. Stewart. "Mantel-Haenszel Analysis of Oxford Data. (i.) Independent Effects of Several Birth Factors Including Fetal Irradiation." **Journal National Cancer Institute** 56: 879-883 (1976).
21. Kneale, G. W. and A. M. Stewart. "Mantel-Haenszel Analysis of Oxford Data. (i.i.) Independent Effects of Fetal Irradiation." **Journal National Cancer Institute** 57: 1009-1014 (1976).
22. UNSCEAR 1977 p.9 paragraph #51.
23. Gofman, J. **Radiation and Human Health,** Sierra Club Books, San Francisco (1981).
24. Blot, W. J. and R. W. Miller. "Mental retardation following in utero exposure to the atomic bombs of Hiroshima and Nagasaki." **Radiology** 106: 617-619 (1973).
25. D'Amato, C. D. and S. P. Hicks. "Effects of low levels of ionizing radiation on the developing cerebral cortex of rats." **Neurology** 15: 1104-1116 (1975).
26. MacMahon, B. "Prenatal X-ray exposure and childhood cancer." **Journal National Cancer Institute** 36: 1173-1191 (1962).
27. Diamond, E. L. et al. "The relationship of intrauterine radiation to subsequent mortality and development of leukemia in children." **American Journal of Epidemiology** 97: 293-313 (1973).
28. Bithell, J. F. and A. M. Stewart. "Prenatal irradiation and childhood malignancy: A review of British data from the Oxford survey." **British Journal of Cancer** 31: 271-287 (1975).
29. Graham, S. et al. "Preconception, intrauterine and postnatal irradiation as related to leukemia." **National Cancer Institute Monograph** 19: 347-371 (1966).
30. Ager, E. A. et al. "An epidemiological study of childhood leukemia." University of Minnesota Medical Bulletin 6: 253-275 (1962).
31. Ford, D. D. et al. "Fetal Exposure to diagnostic X-rays and leukemia and other malignant diseases in childhood." **American Journal of Physiology** 196: 896-898 (1959).

REFERENCES (Continued)

32. Kaplan, H. S. "An evaluation of the somatic and genetic hazards of the medical uses of radiation." **Roentgenology** 80: 696-706 (1958).
33. Polhemus, D. W. and O. Koch. "Leukemia and medical radiation." **Pediatrics** 23: 453-461 (1959).
34. Bross, I. D. J. and N. Natarajan. "Genetic Damage from Diagnostic Radiation." **Journal American Medical Association** Vol. 237, No. 22 (1977).
35. Bross, I. D. J. and N. Natarajan. "Cumulative Genetic Damage in Children Exposed to preconception and Intrauterine Radiation." **Investigative Radiology** Vol. 15, No. 1 (1980).
36. Nash, D. J. and J. W. Gowen. "Effects of X-irradiation upon postnatal growth in the mouse." Biology Bulletin 122: 115-136 (1963).
37. Ershoff, B. H. "Effects of prenatal X-irradiation on testicular function and morphology in the rat." **American Journal of Physiology** 196: 896-898 (1959).
38. Phemister, R. D. et al. "Irradiation of the canine conceptus; Teratogenic, lethal and growth retarding effects." In: **Laboratory Animals in Drug Testing.** Edited by A. Spiegel. pp. 311-323 (1973).
39. Wilson, J. G. "Differentiation and the reaction of rat embryo to radiation." **Journal Cellular Comparative Physiology** 43: 11-37 (1954).
40. Blot, W. J. "Growth and Development Following Prenatal and Childhood Exposure to Atomic Radiation." **Journal of Radiation Research**, Supplement pp. 82-88. Review of Thirty Years Study of Hiroshima and Nagasaki Atomic Bomb survivors (1975).
41. U.S. Health and Human Services Publication FDA 81-8170, August 1981.
42. Meadows, A. T. et al. "Declines in IQ Scores and Cognitive Dysfunction in children with acute lymphocytic leukemia treated with cranial irradiation." **The Lancet**, Nov. 7, 1971.
43. Sternglass, E. J. and S. Bell. "Fallout and the decline of scholastic aptitude scores." Annual meeting of the American Psychological Association. September 3, 1979. Also reported in an Interview with Dr. Ernest Sternglass, **The Phi Delta Kappan**, published by Phi Delta Kappa, pp. 184-187, November 1979.
44. Kochupillai, N. et al. "Down's syndrome and related abnormalities in an area of high back-ground radiation in coastal Kerala." **Nature**: 262 pp. 60-61 (1976).

SECTION IV

APPENDICES

APPENDIX A
RELATIVE BIOLOGICAL EFFECTIVENESS OF PLUTONIUM

Table 44

PROPOSED CONVERSION FACTORS FOR Pu^{239} RELATIVE TO Ra^{226} WITH RESPECT TO BONE CANCER INDUCTION

Source	General (Not derived)	Risk Factors				Q	RBE
		Obs. relative risk in dog	Correction Surface/ Vol. ratio	Correction for Burial time in Bone	Correction Tissue Sensitivity		
ICPR #2 (1959)	5	—	—	—	—	10	50
Marshall and Lloyd (1972) (1)	—	6	—	3	—	10	180
Marshall & Lloyd Correction (1975)	—	16	—	3	—	10	480
MRC (U.K.) (1975) (2)	8	—	—	—	—	10	80
MRC (U.K.) Upper Limit	16	—	—	—	—	10	160
KZ Morgan (1975) (3)	—	15	2	10	4	10	12,000
Mays (1975) (4)	5	—	—	—	—	10	50
Mays Upper Limit	45	—	—	—	—	10	450
Ellet et al. (1975) (5)	30	—	—	—	—	10	300
ICRP #30 (1979)	37	—	—	—	—	10	370
Handbook	-	16	2	3-10	1-4	10	960-12,800

COMMENTS ON THE PROPOSED RBE FACTORS

The ICRP#2 estimate (1959) was originally proposed by ICRP, Committee II: On Internal Doses, with Dr. K. Z. Morgan as Chairperson. Dr. Morgan has since recommended an increase in RBE based on information available now, but not known in 1959.

The Marshall and Lloyd estimates, 1972 and 1975, reflect a change in the risk for dogs based on more precise observations. The 1972 estimate is outdated.

The revision of the HMS(UK) estimate, 1975, from 8 to an upper limit of 16 after review of Dr. K. Z. Morgan's estimate, appears to be an admission of the validity of the observed risk factor for dogs.

Dr. K. Z. Morgan's estimate incorporates the relevant parameters required for extrapolating data on dogs to predictions about humans. There is some dispute about the factor 4, introduced by Morgan on the basis of Metivier's research (6). The baboon lung tissue was shown to be 4 times as sensitive to radiation induced cancer as was dog lung tissue. This would certainly hold true for skin cancers and gastro-intestinal tract cancers as well, since these also involve epithelial tissue. Whether or not this correction factor holds for bone marrow stem cells in unknown, but it would seem prudent to assume that it does until proven otherwise. There is also a question about the appropriateness of using the baboon tissue sensitivity rather than the dog tissue sensitivity when estimating human cancer risk. Again, it is more protective of human health to assume that human tissue is at least as sensitive as baboon tissue.

The RHP-1977 analysis by Cave and Ilberg falsely assumes that Morgan's estimate of plutonium-239 RBE was an upper limit (7). They used instead the earlier estimate of Mays (4), stating that it was a "best estimate" rather than an upper bound. The RHP-1977 also erroneously "corrected" the Morgan RBE by eliminating the factor 4, introduced to correct for tissue sensitivity.

Morgan's RBE estimate may be too low because it did not correct either for non-homogeneous deposition of Plutonium 239 or for population heterogeneity. Therefore his RBE estimate may be too high or too low and can be called a best estimate at this time.

The RBE estimate of Mays et al. is based on the radiobiology of radium-224, which deposits on the surface of bone as does plutonium-239. Mays' research has demonstrated that prolongation of the dose of radium-224, unlike prolongation of X-irradiaiton by fractionalization, increases carcinogenicity. It may imply that animal research at high acute levels of ^{239}PuO underestimates the carcinogenicity of lower chronic doses such as would be experienced after a reactor accident. Mays, after reviewing Morgan's estimate, concluded that a "conservative upper limit" of RBE should not be more than 9 times as large as his 1975 estimate (7). While recognizing the value of this finding, it was the opinion of Morgan that the 50 years of intense research on the radiotoxicity of radium-226 had also provided valuable information which needed to be used for estimating RBE, and information from both lines of research should be utilized (3).

Ellett et al., 1975 (5), did not make a scientific decision relative to choices of RBE for plutonium-239. They merely averaged the following numbers:

ICRP# (1959)	5	
Marshall and Lloyd (1972)	18	
Marshall and Lloyd (1975)	48	
MRC (U.K.) (1975)	8	
K. Z. Morgan (1975)	64	("corrected" by Ellett)
	5 143	

$143 \div 5 = 28.6$ or about 30

Dr. Morgan rejects the "correction". There is general agreement among scientists that the ICRP#2 estimate is incorrect in view of more recent findings. It should not have been included. Including both estimates of Marshall and Lloyd makes little scientific sense. In view of these problems, Ellet's estimate does not add any meaningful information on the RBE of plutonium-239.

The "best estimate" upper and lower values for the RBE of plutonium adopted for this report includes the following risk factors and quality factor:

Observed relative risk in dogs:	16	(8)
Correction surface/volume ratio:	2	
Correction for burial by apposition of new bone:	3 to 10	
Correction for tissue sensitivity:	1 to 4	
Total risk factor:	96 - 1,280	
Quality factor:	10	
Total RBE rems/rads	960 -12,800	

These estimates do not take into consideration the increased carcinogenicity with prolonged dose or the possible change in RBE due to non-homogeneity of dose to bone surface. They are not upper and lower limits, but rather reflect the scientific uncertainty of the values.

A recent publication by Carl Johnson on cancer incidence in a human population exposed to respirable plutonium (9) gives evidence that the true RBE of plutonium may be higher than was assumed in this analysis.

REFERENCES

1. Marshall, J. H. and Lloyd, E. "The Effect of the Remodelling of Bone Upon the Relative Toxicity of Radium and Plutonium in Man and Dog." pp. 421-236 in **Radionuclide Carcinogeneis,** A.E.C. Symposium Series 29. U.S.A.E.C.. Oak Ridge, Tennessee. 1973.
2. Medical Research Council: **The Toxicity of Plutonium,** her Majesty's Stationery Office, London, 1973.
3. Morgan, K. Z. "Suggested Reduction of Permissible Exposures to Plutonium and Other Transuranium Elements." **American Industrial Hygiene Journal** 36: 567. 1975.
4. Mays, C. W. "Estimated Risk from Pu-239 to Human Bone, Liver and Lung." Proceeding IAEA Symposium. Chicago, 1975.
5. Ellet, W. H. et al. "Allowed Health Risk for Plutonium and Americium Standards as Compared to Standards for Penetrating Radiation." Proceedings IAEA Symposium. San Francisco 1975.
6. Metiver, H. et al. "Excretion and Acute Toxicity of $^{239}PuO_2$ in Baboons." **Health Physics** 27:512. 1974.
7. Cave, L. and Ilberg, D. "Relative Hazard Potential — The Basis for Definition of Safety Criteria for Fast Reactors." 1977 pp. 25-28.
8. Mays, C. W. "Risk Estimates for Plutonium-239 in Man." Workshop, Sun Valley, Idaho, 1975.
9. Johnson, Carl J. "Cancer Incidence in an Area Contaminated with Radionuclides near a Nuclear Installation." The Royal Swedish Academy of Science, **AMBIO** Vol. 10, No. 4, 1981.

APPENDIX B
RADIATION DOSE FROM VARIOUS MEDICAL PROCEDURES

The frequency of various medical diagnostic procedures in the U.S. and the estimates of radiation dose to skin, bone marrow and ovary are given. These estimates are quite changeable with equipment, timing, film quality, etc., and estimates for the specific circumstances of exposure are preferred. As a crude estimate, however, which might be helpful for general questions, these dose estimates are included as an appendix to the Handbook.

Table 45

ESTIMATED NUMBER AND RATE OF RADIOGRAPHIC EXAMINATIONS BY AGE AND SEX, UNITED STATES, 1964 AND 1970 (1)

	Number in thousands				Number per 100 persons			
	1964		1970		1964		1970	
Age & Sex	Exams	S.E.	Exams	S.E.	Exams	S.E.	Exams	S.E.
Both sexes	104,987	4,619	129,070	2,904	56.1	2.5	64.6	1.5
under 15	14,865	1,665	16,462	938	25.2	2.8	28.0	1.6
15-29	27,771	2,333	28,637	1,231	59.9	5.0	60.8	2.6
30-44	23,194	2,087	25,849	1,163	66.8	6.0	76.9	3.5
45-64	32,134	2,520	39,443	1,459	85.4	6.7	95.5	3.5
65 & over	11,842	1,516	18,679	1,009	69.2	8,9	98.4	5.3
Male								
under 15	9,095	1,346	9,275	733	30.3	4.5	31.0	2.4
15-29	12,020	1,533	15,131	908	66.5	8.6	67.5	4.1
30-44	11,697	1,497	12,825	846	70.5	9.0	79.4	5.2
45-64	16,776	1,745	17,627	987	92.0	9.6	89.7	5.0
65 & over	4,533	997	8,450	718	60.2	13.2	104.5	8.9
Female								
under 15	5,770	1,096	7,186	661	19.9	3.8	24.9	2.3
15-29	10,751	1,430	13,506	864	53.9	7.2	54.7	3.5
30-44	11,497	1,483	13,025	860	63.5	8.2	74.6	4.9
45-64	15,538	1,678	21,816	1,091	79.4	8.6	100.7	5.0
65 & over	7,290	1,225	10,229	767	76.4	12.8	93.8	7.0

Table 46

ESTIMATED EXAMINATION RATES BY TYPE OF RADIOGRAPHIC EXAMINATION AND SEX, UNITED STATES, 1964 AND 1970 (1)

Type of examination	Number per 100 persons							
	Male				Female			
	1964		1970		1964		1970	
	Rate	S.E.	Rate	S.E.	Rate	S.E.	Rate	S.E.
Skull	1.7	0.6	2.5	0.4	1.5	0.6	1.7	0.3
Cervical Spine	1.1	0.3	1.7	0.4	1.6	0.6	1.5	0.3
Chest								
Radiographic	18.1	2.0	25.3	1.3	16.7	1.8	23.4	1.2
Photofluorographic	8.4	1.3	4.5	0.6	8.9	1.3	5.8	0.6
Thoracic Spine	0.8	0.5	0.7	0.2	0.6	0.4	0.8	0.2
Shoulder	0.8	0.5	1.0	0.3	0.8	4.6	1.0	0.3
Upper Gastrointestinal Series	3.1	1.9	3.4	0.5	2.9	0.8	3.4	0.5
Barium Enema	1.4	0.6	1.6	0.4	1.8	0.7	1.9	0.4
Cholecystography or Cholangiogram	1.2	0.6	1.6	0.4	1.8	0.7	2.4	0.4
Intravenous or Retrograde Pyelogram	2.0	0.7	2.0	0.4	1.5	0.6	1.9	0.4
Abdomen, KUB, Flat Plate	2.2	0.7	1.7	0.4	1.0	0.5	1.9	0.3
Lumbar Spine	2.2	0.7	3.1	0.5	2.1	0.7	2.4	0.4
Pelvis	1.2	0.6	0.8	0.3	1.1	0.6	1.3	0.3
Hip	0.5	0.4	0.4	0.2	0.7	0.5	1.0	0.3
Upper Extremities	4.9	1.1	5.7	0.6	3.4	0.9	4.1	0.5
Lower Extremities	7.0	1.3	6.4	0.7	4.0	1.0	5.7	0.6
Other Abdominal Exams	0.8	0.3	0.6	0.4	1.0	0.5	1.2	0.5
All Other	2.3	0.8	2.7	0.8	1.5	0.6	2.2	0.7

Table 47

TYPICAL X-RAY FACTORS AND SKIN DOSE IN RADIOGRAPHY

Examination	View	kV	MAS	FFD inches	Skin Dose R
Skull	AP	68	60	36	0.6
	Lat.	58	60	36	0.3
	Basal	76	60	36	0.8
Shoulder	AP	68	20	36	0.2
	Lat.	80	100	36	2.0
Chest	PA	86	10	72	0.02
	Lat.	90	30	72	0.07
Abdomen	AP	72	60	36	0.6
Gallbladder	PA, scout	72	60	36	0.6
	PA, spot	78	60	36	0.7
	Lat. decub.	72	60	36	0.6
IVP	KUB, AP	72	60	36	0.6
	Kidneys, AP	72	60	36	0.6
Bladder	AP	72	60	36	0.6
	Lat.	85	400	36	7.7
Upper G.I.	PA	72	90	40	0.9
	Lat.	80	150	40	2.1
Lower G.I.	PA	72	90	40	0.9
	Lat.	84	150	40	2.5
Cervical Spine	AP	64	20	36	0.16
	Lat.	75	10	72	0.04
Thoracic Spine	AP	74	50	36	0.6
	Lat.	80	80	36	1.5
Lumbar Spine	AP	70	80	36	0.85
	Lat.	80	150	36	2.9
Pelvis	AP	66	70	36	0.65
Hip	Lat.	75	150	36	2.3
Femur, lower two-thirds	AP	68	50	36	0.5
Knee	AP, Lat.	55	10	36	0.04
Leg, Lower NS	AP, Lat.	60	100	36	0.5
Foot, NS	AP, Lat.	56	50	36	0.17
Ankle, N.S.	AP, Lat.	60	100	36	0.5
Elbow, Arm,	NS	55	100	36	0.4
Hands, NS		50	50	36	0.12

Table 48

MEAN MARROW DOSES PER RADIOGRAPHIC EXAMINATION IN ADULTS (3)

Examination	(4) Denmark mR (1962)	(5) U.K. mR (1966)	(6) Netherlands mR (1964)	(7.8) U.S.A. mR (1961,1963)
Head	—	36	90	—
Chest 14" x 17"	20	12.5	10	15
Cervical Spine	—	51	8	9
Dorsal Spine	200	208	105	134
Lumbar Spine	100	270	140	330
Pelvis	30	136	138	42
Hip (upper femur)	20	59	47	35
Gallbladder	150	148	36	—
Abdomen	30	126	93	—
IVP	80	518	433	—
Upper G.I.	200	652	80	—
Lower G.I.	200	795	359	—
Cystography	—	557	168	—

Table 49

MEAN ACTIVE BONE MARROW DOSE PER EXAMINATION TO THE ADULT POPULATION (1970) (9)

Examination	Mean active bone marrow dose per examination (mrad)	Annual per capita examination rate	Annual per capita dose (mrad + S.E.)	
HEAD AND NECK				
Skull	78	0.020		1.6 ± 0.1
Cervical Spine	52	0.022		1.2 ± 0.2
Other	—	—		0.6 ± 0.2
THORAX				
Chest-photofluoro.	44	0.073		3.2 ± 0.3
Chest-radiographic	10	0.306		3.2 ± 0.1
Thoracic Spine	247	0.010		2.5 ± 0.4
Ribs	143	0.009		1.3 ± 0.2
Others	—	—		1.9 ± 0.4
UPPER ABDOMEN				
Upper GI Series (total)	535			24.3 ± 4.7
Radiographic (subtotal)	294	0.046	13.5 ± 4.3	
Fluroscopic (subtotal)	241	0.045	10.8 ± 1.9	
Scan	167			
Spot Films	74			
Lumbar Spine	347	0.023		8.1 ± 0.8
Gall Bladder (total)	168			3.7 ± 0.4
Radiographic (subtotal)	129	0.027	3.5 ± 0.3	
Fluoroscopic (subtotal)	39	0.006	0.2 ± 0.3	
Scan	29			
Spot Film	10			
Small Bowel Series	422	0.002		1.0 ± 0.3
Other				2.1 ± 1.0
LOWER ABDOMEN				
Barium Enema (total)	875			21.2 ± 1.8
Radiographic (subtotal)	497	0.024	11.9 ± 1.0	
Fluoroscopic (subtotal)	378	0.024	9.3 ± 1.5	
Scan	268			
Spot Films	110			
IVP	420	0.024		10.1 ± 0.6
Lumbosacral Spine	450	0.013		5.7 ± 0.7
Abdomem KUB	147	0.020		2.9 ± 0.4
Other	—	—		0.4 ± 0.2
PELVIS				
Pelvimetry	595	0.002		1.4 ± 0.5
Pelvis	93	0.012		1.1 ± 0.2
Hip	72	0.009		0.7 ± 0.1
Other	—	—		1.2 ± 0.7
EXTREMITIES				
Femur	21	0.002		0.04 ± 0.02
DENTAL	9.4	0.312		2.9 ± 0.2
			TOTAL	103 ± 5

Table 50

OVARY DOSES PER RADIOGRAPHIC EXAMINATIONS IN ADULTS (3)

Examination	(10) Denmark mR (1963)	(11) Sweden mR (1958)	(12) U.K. mR (1960)	(13) U.S.A. mR (1964)
Head	3.7	0.5	1.9	4
Chest 14" x 17"	4.6	4.1	5.5	8
Chest, miniature	17	1.8	0.1	8
Cervical Spine	1.0	—	1.9	2
Dorsal Spine	7.8	6.2	11.7	9
Lumbar Spine	321	480	405	275
Pelvis	302	200	405	41
Hip	1,322	260	117	309
Femur	168	35	7.3	1
Gallbladder	74	193	299	17
Abdomen	222	1,150	212	289
IVP	744	925	637	407
Upper G.I.	97	29	339	—
Lower G.I.	699	1,520	464	—
Cystography	1,444	1,940	1,285	—

Table 51

ESTIMATED SKIN AND BONE MARROW DOSE FROM DIAGNOSTIC X-RAY PER PLATE TAKEN (U.S.)

Body Area	Skin Dose in mR Average per film		Bone Marrow Dose per film in mrad (1970)
	1960	1970	
Head/Neck	279	300	12.8 - 24.0
Thoracic Spine	1,265	980	10.8 - 65.7
Chest	45	44	0.75 - 6.82
Abdomen	790	960	8.5 - 200.6
Pelvis	829	610	7.93 - 296.46 (to fetus) 5.73 - 53.68
Limbs	117	100	0.17 - 1.2
Dental	1,138	910	0.65 - 2.44

Data in the above table was compiled from:

"Population Exposures to X-ray U.S. 1964" (14)

"Population Exposure to X-ray U.S. 1970 DHEW Publ. (FDA) 73-8047 (15)

"Organ Doses in Diagnostic Radiology" DHEW Publ. (FDA) 76-8030 (16)

"The Mean Active Bone Marrow Dose to the Adult Population of the U.S. from Diagnostic Radiology" DHEW Publ. (FDA) 77-8013 (9)

APPENDIX C
RADIATION DOSES FROM NUCLEAR MEDICINE PROCEDURES

This section contains general information needed to estimate whole body and organ doses in various nuclear medicine procedures. These doses may vary considerably, and specific information on a given procedure at a specific Medical Unit would be preferred. However, this general information may be helpful for answering some questions.

Table 52

BODY WEIGHTS AND ORGAN WEIGHTS FOR VARIOUS AGES (17)

	Organ weight (grams)					
Organ	**Newborn**	**1 year**	**5 years**	**10 years**	**15 years**	**Standard man**
Whole body	3,540	12,100	20,300	33,500	55,00	70,000
Thyroid	1.9	2.5	6.1	8.7	15.8	20.0
Kidney	23	72	112	187	247	300
Liver	136	333	591	918	1,289	1,700
Spleen	9.4	31	54	101	138	150

Table 53

THYROID DOSES FROM ^{131}I (SODIUM IODIDE) IN CHILDREN (18)

			Thyroid Dose	
Age	**Uptake (%)**	**Effective Half-life (days)**	**Observed Rad/μCi Administered***	**Calculated Rad/μCi Administered****
2 days	67	4.7	23.8	32
1 month	10	7.0	5.0	10-32
3 months	9	4.2	2.7	10-32
2 years	10	5.2	2.5	4.3-10
4 years	21	6.3	3.9	4.3-10
6 years	22	4.8	2.4	3.1-4.3
15 years	16	5.9	0.9	1.7

* Based on values measured in this study

** Based on previously reported standard child groups (8)

Table 54

RADIATION DOSES FROM RADIOPHARMACEUTICALS IN CHILDREN

Age	Weight (kg)	Effective Half-life (days)	Whole-Body Doses	
			Observed mrad/μCi Administered*	Calculated mrad/μCi Administered**
		^{51}Cr (Sodium Chromate)		
4 months	8.18	15.0	1.8	4.5
14 months	12.60	20.0	1.7	1.6
5 years	20.0	20.0	1.2	1.0
6 years	13.62	19.4	1.6	0.9
		^{59}Fe (Ferrous Citrate)		
5 years	20.0	38.0	70.3	65
6 years	13.62	31.0	78.0	61
15 years	55.0	39.0	32.0	27

* Based on values measured in this study.
** Based on previously reported standard child groups (19).

Table 55

RADIATION DOSES FROM RADIOPHARMACEUTICALS IN CHILDREN FOR KIDNEY AND BONE

Age	Weight (kg)	Effective Half-life (days)		Doses	
		Te_1	Te_2	Whole body mrad/ μCi Administered	Organ mrad/ μCi Administered
		^{197}Hg (chlormerodrin)			
3 years	14.55	0.8	2.6	0.16	68.1 (kidney)
12 years	47.28	0.9	2.6	0.07	39.0 (kidney)
		^{47}Ca (calcium chloride)			
7 years	25.00	0.7	4.6	2.8	4.5 (bone)
		^{85}Sr (strontium nitrate)			
4 years	15.47	3.5	58.0	16.3	68.3 (bone)
10 years	32.70	1.3	44.0	6.0	40.8 (bone)
12 years	40.00	1.4	53.0	8.6	32.8 (bone)
12 years	60.00	1.5	30.0	2.5	14.0 (bone)
18 years	48.20	3.6	50.0	4.7	27.0 (bone)

Table 56

DOSIMETRY OF TRACER RADIONUCLIDES (20)

Procedure	Radiopharmaceutical	Dosimetry (rads)		
		Patient Dose	Total Body	Critical Organ
Brain Scan	^{99}mTc Pertechnetate	15 mCi	0.20	2-3 (Colon)
	^{203}Hg Chlormerodrin	700 μCi	0.14	40-60 (Kidney)
Liver Scan	^{198}Au Colloid	150 μCi	0.08	5-7 (Liver)
	^{99}mTc-S Colloid	2 mCi	0.03	0.7 (Liver)
Thyroid Scan	^{131}I Sodium Iodide	100 μCi	0.05	130 (Thyroid)
Lung Scan	^{131}I MAA	300 μCi	0.12	2.0
	^{113m} In Fe $(OH)_3$	2 mCi	0.02	1.2
Vitamin B_{12} Absorption	^{57}Co Vitamin B_{12}	0.5 μCi	0.002	0.08 (Liver)
Plasma Volume	^{131}I Albumin	5 μCi	0.010	
	^{125}I Albumin	5 μCi	0.006	
Iron Turnover	^{59}Fe Chloride	10 μCi	0.230	
Renogram	^{131}I Hippuran	20 μCi	0.001	0.02 (Kidney)

REFERENCES FOR APPENDIX B AND APPENDIX C

1. DHEW Publication (FDA) 76-8034. U.S. Department of Health, Education and Welfare 1976.
2. Medical Radiation Information for Litigation. DMRE 69-3. U.S. Department of Health Education and Welfare, 1969, p. 115.
3. ibid, DMRE 69-3, p. 117, p. 116.
4. Buhl, J. in Second Report of the United States Scientific Committee on the Effects of Atomic Radiation. Table 36, p. 407, United Nations, New York. 1962.
5. Radiological Hazards to Patients: Final Report of the (Adrian) Committee, Ministry of Health, U.K., Her Majesty's Stationery Office, London, 1966.
6. Weber, J. Beenmergdosis Tengevolge van de Rontgen-diagnostick. Thesis. University of Leiden, Netherlands, 1964.
7. Epp, E. R., Weiss, H. and Laughlin, J. S. "Measurement of Bone Marrow and Gonadal Dose from the Chest X-Ray Examination as a Function of Field Size, Field Alignment, Tube Kilovoltage and Added Filtration". **Brit. J. Radiol.** 34, 85-100, 1961.
8. Epp, E. R., Heslin, J. M., Weiss, H., Laughlin, J. S. and Sherman, R. S. "Measurements of Bone Marrow and Gonadal Dose from X-Ray Examinations of the Pelvis, Hip and Spine as a Function of Field Size, Tube Kilovoltage and Added Filtration", **Brit. J. Radiol. Sc.**, 247-265, 1963.
9. DHEW Publication (FDA) 77-8013. "The Mean Active Bone Marrow Dose to the Adult Population of the United States from Diagnostic Radiology." Table 6, pp 19-20 (1964 estimates).
10. Hammer-Jacobsen, E. "Genetically significant Radiation Doses in Diagnostic Radiology" **Acta. Radiol.** Supp. 157, Stockholm, 1958.
11. Larsson, L. E. "Radiation Doses to the Gonads of Patients in Swedish Roentgen Diagnostics" **Acta. Radiol.** Supp. 157, Stockholm, 1958.
12. Radiological Hazards to Patients: Second Report of the (Adrian) Committee Ministry of Health, U.K., Her Majesty's Stationery Office, London, 1960.
13. Penfil, R. L. and Brown, M. L. "Genetically Significant Dose to the United States Population from Diagnostic Medical Roentgenology 1964", **Radiology**, 90, 209-216, Feb., 1968.
14. DHEW Publication. "Population Exposure to X-ray United States 1964". Appendix B.
15. Population Exposure to X-ray, U.S. 1970. DHEW Publication (FDA) 73-8047, 1973.
16. Organ dose in Diagnostic Radiology. DHEW Publication (FDA) 76-8030, 1976.
17. Stuart, H. C. and S. S. Stevenson. General factors in the care and evaluation of children. Physical growth and development. Textbook of Pediatrics (7th. ed.) (edited by W. E. Nelson), p. 12. Saunders, Philadelphia (1959).
18. Kereiakes, J. G., H. N. Wellman, J. Tieman and E. L. Saenger. Radiopharmaceutical dosimetry in pediatrics. **Radiology** 90:925, 1968.
19. Seltzer, R. A., J. G. Kereiakes and E. L. Saenger. Radiation exposure from radioisotopes in pediatrics. **New England J. Med.** 271:84, 1964.
20. Burdine, J. A. and K. H. Morgan. Radiation Records-Keeping in Nuclear Medicine. In DMRE 69-3, p. 173 (See Ref. 2).