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INDUCTION OF THYROID CANCER BY IONIZING RADIATION

Recommendations of the
NATIONAL COUNCIL ON RADIATION PROTECTION
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Preface

This report assesses the potential for cancer induction in the thyroid gland after exposure of the gland to external x and gamma radiation and/or some internally deposited radionuclides. Data and assumptions from existing human and animal studies are examined and, where possible, used to develop average risk estimates for populations over various ranges of radiation dose to the thyroid. The carcinogenicity of various iodine isotopes is examined on the basis of available data and conclusions are stated where possible. The carcinogenicity per unit absorbed dose of external x- or gamma radiation and various iodine isotopes are also estimated.

A specific model for risk estimation is developed in this report which involves numerous modifications of an absolute risk model for factors such as age at exposure, sex, ethnic background, source of radiation, exposure range, and time since exposure. The result is considered to represent a practical model which is useful for the purposes of this report. The model derives estimates from the linear portion of the dose response curve and avoids the curvi-linear portion resulting from cell killing. The model is tested using the experience in Marshall Islanders exposed to mixed types of radiation (external gamma radiation and internal emitters).

Risk estimates are presented which are considered to be applicable to the population of the U.S. for mean thyroidal doses in the range from 6 to 1500 rads.

The Council has noted the adoption by the 15th General Conference of Weights and Measures of special names for some units of the Système International d'Unites (SI) used in the field of ionizing radiation. The gray (symbol Gy) has been adopted as the special name for the SI unit of *absorbed dose, absorbed dose index, kerma, and specific energy imparted.* The becquerel (symbol Bq) has been adopted

as the special name for the SI unit of *activity* (of a radionuclide). One gray equals one joule per kilogram; and one becquerel is equal to one second to the power of minus one. Since the transition from the special units currently employed—rad and curie—to the new special names is expected to take some time, the Council has determined to continue, for the time being, the use of rad and curie. To convert from one set of units to the other, the following relationships pertain:

$$1 \text{ rad} = 0.01 \text{ J kg}^{-1} = 0.01 \text{ Gy}$$

$$1 \text{ curie} = 3.7 \times 10^{10} \text{ s}^{-1} = 3.7 \times 10^{10} \text{ Bq (exactly).}$$

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Contents

1. Introduction

The purpose of this report is to evaluate the potential of exposure to x and gamma external radiation and/or to internally deposited radionuclides to induce thyroid cancer in humans. Any such effort is necessarily subject to the constraint of limited data, and this is particularly true for radionuclides deposited in the thyroid. What human data exist relate primarily to exposure to external x-irradiation or, to a much lesser degree, to internally deposited ^{131}I. In spite of such limitations, practical protection procedures require a quantitative assessment of the potential of radiation exposure to induce human thyroid cancer. That potential is most often expressed in terms of the risk of developing radiation induced thyroid cancer.

To develop risk estimates, it is necessary to examine the reports and assumptions from existing human and non-human studies. However, the transfer of inferences from animal studies to humans is perilous. In addition, large gaps in the existing data, the low incidence of thyroid cancer, and the small size of populations available for study make risk derivations uncertain. At best, the potential of radiation exposures to cause human thyroid cancer can only be approximated.

This report makes use of such data as are available to develop average risk estimates for combined populations over various ranges of radiation dose to the thyroid. The estimates are not intended and should not be used for application to individuals. Their use in any circumstances requires understanding and careful consideration of their limitations and must include evaluation of a large number of often ill-defined factors such as type and amount of exposure, time since exposure, and differences of sex, age and heredity.

Since most available data on the induction of cancer by radiation are obtained from populations that received relatively large exposures, extrapolation to lower dose levels is often necessary. However, large exposures often cause cell death which can influence the incidence of observed carcinogenesis. For this reason, the dose ranges used for the calculation of risk are confined to situations in which human thyroidal carcinogenesis has been demonstrated and for which cell killing is not thought to be a serious limiting factor.

2. The Development of A Suitable Risk Estimate Model

2.1 Introduction

The linear no threshold model has been considered appropriate for the evaluation of radiation carcinogenesis in the thyroid (Bond, 1979), and this report attempts to develop risk estimates utilizing a linear dose-response model over a specific dose range. While the linear dose-response model is only an approximation, it does express the average risk per unit of radiation dose over the entire fitted dose range (Land, 1980).

The specific risk estimate model used in this report involves numerous modifications of an absolute risk model based on age at exposure, sex, source of radiation, dose range under consideration, and requires restriction of use to populations of similar heredity. The result is a model that does not conform to traditional "absolute" or "relative" models but represents a practical compromise for the defined purpose of this report.

The starting point for the specific risk estimate model is the absolute risk coefficient. In its simplest form, the absolute risk coefficient is calculated according to the following equation:

$$R = \frac{C}{n} \cdot \frac{10^6}{D \cdot y} \tag{2-1}$$

Where:

R = absolute risk coefficient: the number of cases attributable to radiation exposure per million person-rad-years at risk,

C = the number of cases attributable to radiation exposure,

n = the number of subjects at risk in the irradiated population,

D = the average radiation dose (rads) to the thyroid, and

y = the average number of observed years at risk per subject.

Detailed discussions of the various components in the equation are presented and appropriate qualifying statements are given for each risk estimate developed.

2.2 Dose Response Relationships For Thyroid Cancer

Several studies have examined the dose-response relationship for human thyroid cancer. Various factors in human thyroid cancer induction by external x irradiation have been evaluated by Shore *et al.* (1980). They analyzed the pattern of thyroid cancer 5 to 39 years post-treatment in a group of 2,653 people irradiated for an enlarged thymus in childhood. Both a "highly significant linear component and also a significant quadratic component" of the dose-response curve were noted, although the authors indicated that the precision was limited because of the small number (24) of cases of thyroid cancer. The deviation of the calculated linear regression slope from the observed values was small at low doses. However, the risk in lower dose groups appeared to be overestimated by a factor of about 2.3 by a strictly linear model derived from the entire population. When the population was divided into two groups representing approximately equal person-rad-years at risk, those who received from 400 to 1050 rads to the thyroid had a higher risk estimate (by a factor of about 1.8) than that calculated for the group receiving less than 400 rads. For many cases in the higher dose group, the doses were partially fractionated and there appeared to be some direct relationship between dose per fraction and cancer yield. Therefore, the observed dose-response relationship may not represent that which would result following a single acute exposure. Potential errors in the linear absolute risk model will vary depending on the dose range being fitted. Nevertheless, these data suggest that, for doses in the range of about 20 to 1000 rads, a linear model may best approximate risk over the range from 50 to 600 rads, while possibly underestimating risk at the high end of the range (>600 rads) and overestimating risk at the low end of the range (<50 rads).

Wakabayashi *et al.* (1983) examined the occurrence of thyroid cancer in Nagasaki in an attempt to clarify the shape of the dose response curve for thyroid cancer. The majority of persons studied received a dose that was less than 10υ rads. After tests of linear, quadratic, and linear-quadratic models, they concluded that the linear model produced the best fit for the data, but noted that they could not distinguish

statistically one model from the other.

For most of the internal emitters under consideration in this report, there are little available data from human studies. Where human data are limited, information from human exposure to external radiation, radiobiologic studies in animals, and the basic sciences are used to develop or to quantify the risk estimates for internal emitters. The bulk of human experience has been with exposure to external radiation or to ^{131}I, so emphasis is placed on the development of risks for exposure to external gamma or x ray sources and to ^{131}I, followed by a classification of other isotopes of iodine and ^{99m}Tc as either "external radiation like" or "^{131}I like" in terms of their predicted effects on the human thyroid gland.

2.3 Determination of the Number of Thyroid Cancer Cases Attributable to Radiation

Ideally, the determination of the number of thyroid cancer cases in an exposed population that may be attributable to a particular radiation exposure [C in Eq. (2–1)] would utilize a comparison with a population identical in all other respects to the exposed population, but lacking the exposure being studied. The identical character of the two populations would extend to medical, natural background, and incidental radiation exposures (other than the one being assessed) and to other factors thought to be related to thyroid disease, including, but not limited to: age; duration and methods of observations; sex; familial, ethnic, and environmental influences; diseases; and medical intervention. Such control groups for comparison have not been available for many studies assessing radiation effects.

To prepare the risk estimates, information from studies of human exposures to ^{131}I and to external radiation is utilized, and data from several different populations irradiated under various circumstances are combined. Because many of the available data had been drawn from diseased populations, an attempt is made to adjust them, whenever possible, for the spontaneous occurrence of thyroid lesions observed in non-irradiated cohorts whose environments and/or existing diseases are similar to the irradiated cohorts. Data drawn from irradiated populations for whom no specific non-irradiated controls are reported have been adjusted for the spontaneous prevalence of thyroid disease in the general population.

2.3.1 *Thyroid Cancer in Patients with Graves' Disease Not Treated with ^{131}I*

Dobyns *et al.* (1974) reported that 1553 of 10,014 (15.5%) patients with surgically-treated Graves' disease had palpable thyroid nodules noted prior to or during surgery. The mean age of the patients was 40.1 years; over 95 per cent were older than 20 years at the time of diagnosis. In 9 of the 1553 patients, the palpable nodules were thyroid cancer; the remaining nodules were benign on histological examination. Based on these surgical findings of 9 cases in 10,014 patients, the spontaneous prevalence of palpable thyroid cancers in patients with Graves' disease is calculated to be approximately 0.1 per cent.

2.3.2 *Thyroid Cancer in the General Population*

In studies of thyroid cancer the yield reflects the clinical and pathologic efforts expended in detection. For estimating the spontaneous occurrence of thyroid nodules and thus of clinically important thyroid cancer in the general population, only clinically evident disease is included. There is no attempt to take into consideration the problem of so-called "occult" thyroid cancer which, with rare exception, is only incidently noted by the pathologist (Sampson *et al.*, 1969; Sampson, 1976). Because tumor registry data will underestimate the actual prevalence of disease, studies containing data relating to the spontaneous prevalence of clinically detectable nodules in the general population were examined.

Data from work by Tunbridge (1982) on the prevalence of clinically detectable thyroid nodules in an adult English population of 2779 people 18 years of age or older were combined with similar data from the Framingham study (Vander *et al.*, 1968) of 5127 adult Americans between the ages of 30 and 65 years to estimate the spontaneous prevalence of palpable thyroid nodules (Maxon *et al.*, 1977) in a predominately Caucasian population of European ancestry. Palpable nodules were found in approximately 8.9 percent of the women and in about 1.8 percent of the men. In addition, Mortensen *et al.* (1955) found that about 5 percent of 887 patients at a median age of 60 years had palpable nodules on clinical evaluation.

Rallison *et al.* (1975) examined 2271 children in Arizona as a control group in their evaluation of people exposed to atomic fallout. The children ranged in age from 11 to 18 years and had no known exposure to radiation. Palpable thyroid nodules were found in 33 of the children (1.5 percent). A survey of 7785 school children from Michigan, Ken-

tucky, Georgia and Texas from 9 to 16 years of age found 4 definite thyroid nodules and 13 possible nodular glands, for a total of 0.22 percent (Trowbridge *et al.*, 1975).

A linear regression function was fitted to the age-group specific incidences calculated from each of the studies cited in order to have a large data base including all ages. Based on findings of Messaris *et al.* (1973), ten percent of the nodules were assumed in the current report to be malignant in calculating the number of expected cancers from the total numbers of observed thyroid nodules in people below age 20, and a rate of 12 percent was used for people over age 20. The resultant estimate of the spontaneous incidence of clinically detectable thyroid cancer is 0.01 percent per year for the general population (Maxon *et al.*, 1977).

Data from the Third National Cancer Survey carried out at about the same time indicate that the overall age-adjusted incidence of thyroid cancer for both sexes, all ages and races combined, is 3.6 per 100,000 population or 0.0036 percent for those geographic locations represented in both the Second and Third National Survey (Third National Cancer Survey, 1975). The difference between the estimated thyroid cancer incidence based on clinical examinations (0.01 percent per year) and the incidence in the National Survey (0.0036 percent per year) suggests that registry data may underestimate the true incidence in the general population by a factor of about three. The projected clinical incidence of 0.01 percent per year is used when the incidence of thyroid cancer in non-irradiated control groups is not reported.

2.4 Minimum Induction Period for Thyroid Cancer

In all studies of radiation associated solid (non-leukemic) cancers there has been some period of time between radiation exposure and the detection of the first cancer during which no malignancies were noted. This period of time, referred to as the minimum induction period (Fig. 2.1), has generally been considered to be between 5 and 15 years for solid cancers (Land, 1980).

Beach and Dolphin (1962) and Raventos *et al.* (1964) examined a total of 660 cases of thyroid cancer occurring after external radiation in childhood. Based on these data, the times from radiation to detection of the cancer had a log-normal distribution with a cumulative frequency which showed a rapid increase to a plateau about 15 to 25

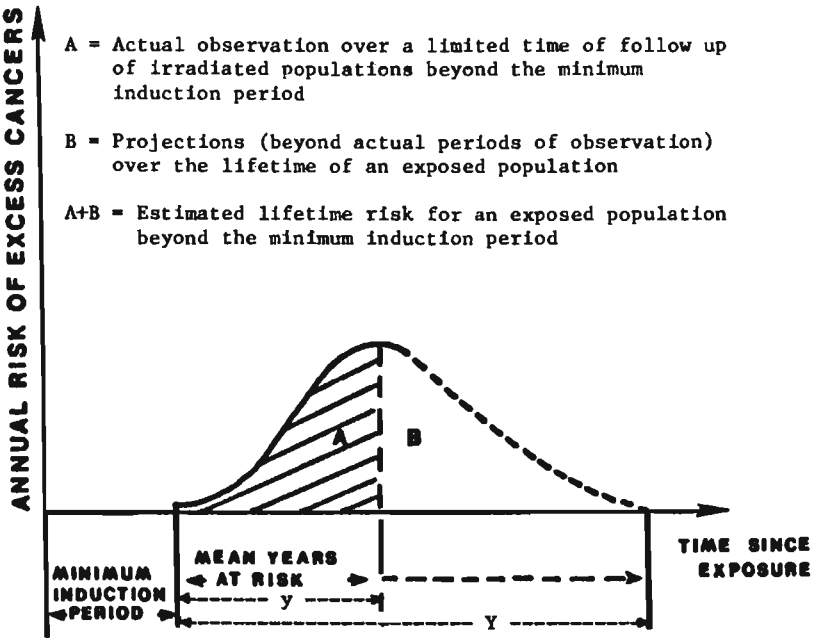

Fig. 2.1 Annual risk of excess cancer versus time since exposure.

years after exposure. When data on the 660 individual patients were combined, the mean time of appearance of thyroid cancers was 10.5 years with two standard deviation limits of 3.6 to 30.8 years. The follow-up on these patients was limited, which may have resulted in shortening of the estimated mean time from exposure to the development of the cancer (Shore *et al.*, 1980). On the other hand, the time interval from irradiation to detection of the cancer is longer than the interval between irradiation and the initial growth of the neoplasm. In a group of patients with thyroid cancers following external radiation in childhood, Winship *et al.* (1970) found, retrospectively, that the average interval between early clinical evidence of a cancer and its confirmation at surgery was almost 2 years. Thus, studies that do not follow patients prospectively from the time of irradiation to the detection of the cancer may overestimate the minimum induction period for thyroid cancer.

Data from the Marshallese followed prospectively after exposure to atomic fallout (Conard *et al.*, 1984) indicate that thyroid cancers first appeared 8 years following exposure. In a study of Japanese survivors of the atomic bombs, Kato and Schull (1982) reviewed non-thyroidal

cancers and found that solid cancers attributable to radiation occurred only 5 years or more after exposure. There was no relationship between radiation dose and induction period in the Japanese.

In Rochester, New York (Shore *et al.*, 1980) and in Cincinnati, Ohio (Saenger *et al.*, 1960; Maxon *et al.*, 1980), the earliest thyroid cancers found in people who were irradiated in childhood were diagnosed more than 6 years after exposure. In Chicago, Illinois (Roudebush *et al.*, 1978) 6 of 91 (6.6 percent) of the thyroid cancers found in a group of radiation-treated patients occurred within 10 years after exposure. Shore (1984) reviewed this question of a minimum induction period for thyroid cancer following radiation to the thyroid and concluded that 5 years is a reasonable estimate based on human data.

Based on the above observations, a minimum induction period of 5 years will be used in the calculation of risk. The 5 years will be subtracted from the mean follow-up time reported in determining person-years at risk.

2.5 Average Time at Risk and Duration of Risk

It is difficult to determine the average number of observed years at risk to be used in the calculation of risk coefficients [y in Eq. (2-1)]. The difference between the mean amount of time elapsed between radiation exposure and detection of the cancer, on the one hand, and the minimum induction period for thyroid cancer of 5 years, on the other, is assumed to represent the number of years at risk in groups of patients with proven thyroid cancer. If no cancer is detected, the difference between the time interval from exposure to the follow-up examination and the minimum induction period of 5 years is used as the number of years at risk. In cases of multiple exposures over long periods of time, the mean time between the first and the last exposure is taken as the time at which the total exposure occurred.

The duration of risk for the induction of thyroid cancer following radiation exposure [Y in Eq. (11-1)] has not been defined because of the limited follow-up time of most studies. Shore (1980) has shown that for people exposed in childhood there appears to be a continuing occurrence of excess thyroid cancer cases from 5 to 40 years after irradiation. Goolden (1958) has reported the occurrence of thyroid cancer as long as 40 years after irradiation, although De Groot *et al.* (1983) have reported data that provide evidence for the possibility that there may be as much as a 60 percent decrease in risk after 40 years post-irradiation. Similarly, in the most recent survey of the thymus-irradiated children in Rochester, New York (Woodard, 1980), the risk for new thyroid cancer 25 to 33 years post exposure was only

TABLE 2.1—*Years at risk for age and sex subgroups of the general population of the United States in 1980*

Parameter	Age Group			
	>18 y		≤18 y	
	M	*F*	*M*	*F*
1. Number	75,317,594	83,221,472	34,735,567	33,271,172
2. % Total U.S. Population[a]	33.3	36.7	15.3	14.7
3. Median Age (Years)	38.6	41.4	9.2	9.3
4. Mean Life Expectancy for Median Age Group (Years)	34.4	38.1	61.3	68.8
5. Mean Years at Risk (Life Expectancy Minus 5 Year Minimum Induction Period)	29.4	33.1	56.3	63.8
6. Total (Lifetime) Years at Risk for Each Subgroup Per Million People in General Population	9.79×10^6	12.15×10^6	8.61×10^6	9.38×10^6
7. Fraction of Total Person Years at Risk for the General Population Contributed By Each Age/Sex Group	24.5%	30.4%	21.6%	23.5%

[a] Size of Total U.S. Population: 226,545,805 people with average lifetime years at risk of 39.93 years per person.

about 40 percent of the risk from 5 to 25 years post-exposure. All of these data are based on people receiving x irradiation for benign disease in childhood at doses below 2000 rads and suggest, for such exposures, that an assumption of an average total duration of risk of more than 40 years may overestimate the lifetime risk for people exposed in childhood.

Because the number of years at risk is different among age and sex groups, the age and sex distribution of the general population in the United States was determined based on the 1980 Census (U.S. Department of Commerce, 1983). Median ages for subgroups were calculated by linear interpolation. Mean life expectancies for the median age in each subgroup were determined from vital statistics for the United States in 1978 (U.S. Bureau of the Census, 1983) using a weighted age-race-sex calculation and interpolating for the "tenths" of a year in each age group. The results are shown in Table 2.1. The minimum induction period of 5 years has been subtracted from the mean life expectancy in each group to determine the mean years at risk. To calculate the lifetime risk per million people in the general population of the United States, the mean years at risk for each age-sex subgroup (Table 2.1) will be used in this report.

3. Thyroid Cancer Following External Radiation Exposure

3.1 Dose Levels at Which Cell-Killing Appears Dominant over Carcinogenesis

In a review of 4673 patients treated with external irradiation in childhood, Beach and Dolphin (1962) found that none of the 23 patients with carcinoma had received more than 1270 rads to the thyroid. Although only 12 of 4673 patients could be shown definitely to have received more than that dose, the authors suggested that, at doses above 2000 rads, thyroid neoplasms would probably not be induced by external irradiation of the thyroid due to cell killing.

Hanford *et al.* (1962) found thyroid cancer in 7 of 162 patients who had received external x irradiation for tuberculous adenitis. No thyroid cancer had developed in 8 patients who had received more than 1600 rads at a mean follow-up time of 17 years. At a mean follow-up time of 22.5 years, DeLawter *et al.* (1963) similarly found no thyroid cancers in 222 patients who had received a mean x-ray dose to the thyroid of approximately 2100 rads. The majority of these patients had been treated for goiter. Although Wilson *et al.* (1958) reported 2 cases of thyroid carcinoma after doses possibly higher than 2000 rads, accurate dosimetry was not available. In reviewing earlier data on the carcinogenic potential of large doses of x-irradiation to the human thyroid gland, Saenger *et al.* (1963) concluded that thyroid cancer may develop rarely in patients so exposed.

A recent report (Pretorius *et al.*, 1982) has indicated a total of 6 cases of thyroid cancer in patients with other underlying neoplasms who were treated with high dose (>2500 rads) external radiation therapy to the neck. The total number of subjects at risk in this series is unknown.

Kaplan *et al.* (1983) performed thyroid evaluations in 95 patients who had received external radiation therapy to the neck region for childhood cancer 5 to 34 years earlier with a mean follow-up time of 19 years since radiation. None of the 95 patients was known to have had abnormal thyroid function prior to evaluation and none had evidence of recurrence of their primary cancer. The approximate median thyroidal dose was 3000 rads with a range of <1 to 8250 rads.

Eighty-three patients had also received chemotherapy; 41 had undergone lymphangiography with iodinated contrast media prior to radiation therapy; none had received thyroid hormone. Twenty-six patients were found to have thyroid nodules, and 10 of these were referred for thyroid surgery. A total of 3 thyroid cancers were found; two of these were apparently very small and only incidentally noted. Radiation doses to the thyroid glands of the 3 patients were 820, 900, and 3100 rads. If the single cancer 1 cm or more in size in the 10 patients operated on were representative of the 26 patients with nodules, a maximum of 3 such cancers might be predicted for the entire group of 95 patients resulting in an approximate risk of 0.8 cases/10^6 persons per rad per year at risk, assuming a minimum induction period of 5 years and a mean follow-up time since irradiation of 19 years. On the other hand, functional thyroid damage manifest as biochemical hypothyroidism was found in 42 of 95 subjects (44 percent) with a significant correlation between thyroidal radiation dose and the degree of biochemical abnormality. These data suggest that at doses around 2000-3000 rads, cell killing and hypothyroidism predominate over carcinogenesis.

In summary, at external radiation doses of more than 1500 to 2000 rads and mean follow-up times up to 22.5 years, the risk of radiation-associated thyroid carcinogenesis seems to be less than at lower doses, probably due to a dominance of cell-killing or sterilization at higher dose levels. A linear risk extrapolation from information obtained solely at high dose levels would underestimate the risk per rad at lower dose levels.

In order to decrease the effect of doses that are potentially lethal to the thyroid cell on estimates of the risks of carcinogenesis, only exposures to the thyroid of less than 1500 rads will be considered in formulating risk estimates.

3.2 Thyroid Cancer After Exposure to External Radiation of Less Than 1500 Rads

North American Experience

The majority of human experience relating to thyroid cancer induction is in people treated with external x irradiation in childhood for benign disease. The largest North American series are those of Hempelmann *et al.* (1975) in Rochester, of Maxon *et al.* (1980) in Cincinnati, of Shore *et al.* (1976) in New York City, and of Frohman *et al.* (1977) and De Groot *et al.* (1983) in Chicago.

The University of Rochester study compared 2872 young adults who had been given x-ray therapy for presumed thymic enlargement in infancy to 5055 non-irradiated siblings. Mean thyroidal exposures ranged between 17 and 685 rads for the various cohorts in the study, with an average exposure of 119 rads. Follow-up was obtained using 4 mail surveys between 1953 and 1971. The mean number of years of follow-up was 24.2 for the irradiated and 22.9 for the non-irradiated subjects. Twenty-four thyroid cancers were found in the irradiated group, compared to none in the controls. Sex seemed to influence risk since the male-female ratio in the patients with cancer was about 0.4 compared to a ratio of 1.4 for the entire cohort. The study included one subgroup (Group C) of 261 irradiated persons who had received relatively higher radiation doses, had been followed longer, and had a much higher proportion of Jewish subjects. Altogether, this subgroup of 261 persons contributed 13 of the 24 thyroid cancers found. Hemplemann also noted that 11 of the 24 cases were present in the 8 percent of the total population at risk which was Jewish. The relative risk for Jews compared to non-Jews was about 3.5 even after adjustment for sex, time since irradiation, and radiation dose (Shore *et al.*, 1980). For the group as a whole, the absolute risk was about 3.8 cases per million persons per rad per year at risk. If the Jewish subjects were excluded, the absolute risk of thyroid cancer was about 2 cases per million persons per rad per year at risk (Shore *et al.*, 1980). In preliminary reports of a subsequent survey from 1979–1980, an additional 5 thyroid cancers were found in the irradiated group over the intervening 8 years compared to 1 new case in the control group (Woodard, 1980). Thus, the approximate absolute risk over this 8 year period beginning about 25 years post irradiation would be 1.6 cases per million persons per rad per year at risk.

In the University of Cincinnati study, 1266 subjects who received external radiotherapy for a variety of benign diseases in childhood were compared to 958 age-, sex-, race-, and disease-matched people who had received non-radiation therapies. In addition, a comparison of 9865 family members of the two cohorts revealed no evidence of a familial bias toward thyroid disease in the irradiated group. Follow-up was via interviews conducted by specially trained registered nurses, with a mean follow-up time of 21.5 years. The mean thyroid radiation dose to the irradiated cohort was approximately 290 rads. A total of 12 thyroid cancers were found in the 1266 subjects, and 1 was found in the 958 controls, for an excess of 11 cases in the irradiated group. The mean estimated total radiation dose to the thyroid for subjects with thyroid cancer was 524 rads, with a median value of 390 rads and

a range of 210 to 1120 rads. The male-female ratio in the thyroid cancer patients was 0.6, compared to a value of 1.3 in the overall irradiated cohort. The irradiated men with thyroid cancer had about a 20 percent higher mean thyroidal dose than irradiated women with thyroid cancer, and their mean time post exposure (15.7 years) was somewhat shorter than that of the women (22.7 years). The entire study population, drawn from religious-affiliated hospitals other than the Jewish Hospital and from the charity hospitals, was predominantly non-Jewish and Caucasian. The absolute risk for thyroid cancer was 1.8 cases per million persons per rad per year at risk.

In New York, Shore *et al.* (1976) evaluated 2215 subjects treated in childhood with irradiation for *tinea capitis* and compared them to 1395 non-irradiated control subjects who had had *tinea capitis*. Thyroid doses were estimated to be about 4 to 8 rads (mean calculated to be 6 rads) and the average interval of follow-up was about 20 years. No thyroid cancers were found in the irradiated group. The irradiated cohort in this study contained approximately 24 percent black and 11 percent Jewish subjects.

At the Michael Reese Hospital in Chicago, individuals were identified as having received external radiation to the head, neck, or chest prior to or during adolescence. Of this group, 2189 of 5226 were contacted and judged to have adequate data for inclusion in the study. A total of 1476 out of the 2189 subjects were actually examined and were considered representative of the entire study group. The mean follow-up time was about 28 years (Frohman *et al.*, 1977). The total population was reported to have received an average thyroidal dose of 808 rads. About 90 percent were less than 10 years of age at exposure. No control (non-irradiated) population was evaluated. Surgery was recommended for 402 patients, of whom 327 subsequently received the operation. Of the total 92 cancers found in the 327 subjects undergoing surgery, 31 (34 percent) were 5 mm or less in diameter. Such cancers are rarely fatal (Sampson, 1976) and are considered to have little clinical importance (Sampson *et al.*, 1969). If lesions less than 5 mm in diameter which were only incidentally noted at surgery for other reasons are excluded, then one can predict that about 75 cancers [[(92-31)÷327][402]] greater than 5 mm in diameter would be found in the group of 402 irradiated subjects for whom surgery was recommended. Based on the calculations of the prevalence of clinically evident thyroid cancer in the general population aged 20 to 29 years, 3–4 clinically detectable thyroid cancers would be expected for a radiation associated excess of about 70 cases. The resultant absolute risk in the population of 1476 people is about 2.6 cases per million persons per rad per year

at risk. No correlation was observed between age at exposure or sex and the subsequent development of thyroid cancer. Although not mentioned in the report by Frohman *et al.* (1977), the population in the Michael Reese study had a high proportion (about 80%) of Jewish patients and less than 1 percent non-caucasian patients (Frohman, 1983).

A University of Chicago study (De Groot *et al.*, 1983) evaluated 416 subjects who were referred with a history of prior head or neck irradiation for benign, non-thyroidal disease in childhood. About 263 of 416 (63 percent) of the patients had also been considered by the referring individual to have possible thyroidal abnormalities and thus are highly selected. The total number of irradiated people from whom these patients were selected is unknown, precluding the use of these data for the derivation of numerical risk estimates. However, the data provide insight into other aspects of human thyroid carcinogenesis. The mean age at irradiation was 7.1 years with a mean thyroidal dose of 451 rads. The average time between exposure and examination was 26.4 years. Thyroid cancers were found at surgery in 41 people, and 35 of the cancers were greater than 5 mm in diameter. A prospective followup was initiated of a subgroup of 130 patients whose initial examination did not indicate cancer. The incidence of new cancer cases appeared to decline: the risk in the subgroup was about 30% of that calculated for the total group. This observation may reflect the prior patient selection and/or a true decline in the incidence of thyroid cancer with time following irradiation. Among 391 patients examined up to 40 years after exposure, 40 cancers were found (10.2 percent); among 25 patients examined 40 years or more after exposure, only 1 cancer (4 percent) was found. The average time interval between irradiation and examination for patients with thyroid cancer was 23.8 $\pm$ 7.0 years (range 10 to 40 years), and less than 1 percent of the patients were examined within the first 10 years after exposure.

When the results of several studies from the United States are combined (Table 3.1), an excess is found of 109 thyroid cancers in 7829 subjects, representing about 43 million person-rad-years at risk (range of mean years follow-up is 20 to 35 years and range of mean thyroidal dose is 6 to 808 rads). Their composite absolute risk is about 2.5 cancers per million persons per rad per year with a risk range (based on the risks calculated for each individual study) of 0 to 3.0 thyroid cancers per million persons per rad per year in children exposed to external radiation to the thyroid. The approximate ethnic and sex composition of the irradiated subjects in these studies is shown in Table 3.2. While the high proportion of males would tend to lower

TABLE 3.1—*Thyroid cancer following head and neck x-irradiation for benign disease in childhood in the United States*

Source	Number Irradiated	Excess Thyroid Cancers[a]	Mean Years At Risk[b]	Mean Thyroidal Dose (Rads)	Total Person-Rad-Years At Risk
Shore *et al.* (1976)	2,215	0	15	6	199,350
Hempelmann *et al.* (1975) and Woodard (1980)	2,872	28	27	119	9,227,736
Maxon *et al.* (1980)	1,266	11	16.5	290	6,057,810
Frohman *et al.* (1977)	1,476	70	23	808	27,429,984
	7,829	109	21.2[c]	245[c]	42,914,880

[a] Clinically evident disease

[b] Assuming a minimum induction period of 5 years

[c] Weighted (by number irradiated), mean years at risk is 21.2; weighted mean thyroidal dose is 245 rads. The composite absolute risk coefficient is 2.5 cancers per million persons per rad per year at risk.

TABLE 3.2—*Approximate ethnic composition of the population of irradiated children in the United States*

Source	Number Irradiated	% Caucasian Jewish	% Caucasian Non-Jewish	% Black	% Male
Shore *et al.* (1976)	2,215	11	65	24	87
Hempelmann *et al.* (1975)	2,872	8	91	1	58
Maxon *et al.* (1980)	1,266	2	90	8	57
Frohman *et al.* (1977, 1983)	1,476	80	20	<1	60
Total	7,829	22	69	9	66

the risk estimate, this would be offset by the apparent increased risk for the Jewish subjects found in the Rochester, New York study.

Israeli Experience

Ron and Modan (1984) examined tumor registry data for 10,842 subjects who had received x irradiation of the head for *tinea capitis* in Israel at a mean age of 7.1 years. The mean follow-up time was 22.8 years, and comparison was made to the same number of non-irradiated, non-siblings and to 5400 siblings without known radiation exposure. Thyroid cancers were found in 29 of the irradiated group, compared to 8 in the larger, combined control group, resulting in a calculated

excess of 24 cases in the irradiated population. Subjects in this study had an estimated mean thyroidal dose of 9 rads with a range of 4.3 to 16.9 rads. The absolute risk for thyroid cancer in this Jewish population was about 14 cases per million persons per rad per year at risk; 23 of the 29 total thyroid cancers in the irradiated group occurred in women, as did 6 of 8 cancers in the non-irradiated controls. The 5420 subjects who were of Moroccan or Tunisian descent were found to have about twice the absolute risk of thyroid cancer as the 5422 subjects from Israel, Asia, and other North African areas.

Japanese A-Bomb Survivors

Since 1945, Japanese survivors of the atomic bombs detonated in Hiroshima and Nagasaki have been followed for long term health consequences of their radiation exposures. The resulting data have been complicated by uncertainties in the radiation dosimetry. Most of the uncertainty has been centered around neutron dosimetry, primarily involving the people in Hiroshima. In the case of Nagasaki, over 90 percent of the exposed population had calculated neutron doses to the thyroid of less than 0.5 rads, and neutrons were considered to be responsible for less than 5 percent of their total thyroidal dose. In addition, the tumor registry data are quite complete in Nagasaki for the 20 year period from 1958 to 1979, representing an interval of 13 to 33 years following exposure. Several recent reports on thyroid cancer in the people of Nagasaki provide useful information regarding sex, age, and dose-response characteristics of thyroid carcinogenesis following high dose rate external gamma irradiation of the human thyroid.

Prentice and associates (Prentice *et al.*, 1982) analyzed data of clinically-evident thyroid cancer (about 60 percent of total thyroid cancers in this registry) during the period from 1959 to 1979. The registry included 23,884 people who were residents of Nagasaki in 1945, who were still alive in 1959, and who had no documented evidence of thyroid cancer prior to 1959. Radiation doses to the thyroid were based on the so-called T65 dose estimates and were fairly evenly distributed throughout population subgroups derived according to age at exposure and sex (Table 3.3). When excess thyroid cancers are calculated according to age group at exposure and sex, there are apparent differences in the incidence of excess cancers (Table 3.4). These data suggest that women are more susceptible than men and younger people more susceptible than older people. The differences in susceptibility do not appear to be due to differences in radiation dose.

Using the T65 revised dose estimates Wakabayashi *et al.* (1983) also examined the population from Nagasaki. They concluded that the

TABLE 3.3—*Distribution of thyroidal doses by age and sex in 23,884 residents of Nagasaki, Japan, based on T65 dose estimates*[a]

Sex Group	Age Group in 1945	Approximate Thyroidal Dose (rads)			
		0	1–49	50–99	100+
Females	<30	40.6%[b]	44.7%	5.7%	9.0%
	>30	36.5	53.8	4.0	5.7
	All	39.3	47.6	5.2	7.9
Males	<30	40.5	46.0	5.3	8.2
	>30	44.3	40.1	6.5	9.1
	All	41.8	43.9	5.8	8.5

[a] Adapted from Prentice *et al.*, (1982)

[b] All numbers are expressed as a percent of the total population in the specified age and sex group.

TABLE 3.4—*Clinically evident thyroid cancers in 23,884 residents of Nagasaki, Japan detected during the two decades from 1959 to 1979*[a]

Sex Group	Age Group in 1945	Cancers/Population		Excess Cancers per 10^6 Exposed Persons[b]
		Unexposed	Exposed	
Females	<30	4/3751	21/5490	2759 ± 991
	>30	5/1587	9/2766	103 ± 1778
	All	9/5338	30/8256	1948 ± 869
Males	<30	2/2683	5/3949	521 ± 773
	>30	2/1621	2/2037	−252 ± 1114
	All	4/4304	7/5986	240 ± 642
Both	<30	6/6434	26/9439	1822 ± 661
	>30	7/3208	11/4803	108 ± 1076

[a] Adapted from Prentice *et al.*, 1982.

[b] Excess cancers per 10^6 exposed persons ± one standard deviation calculated using a Poisson distribution.

linear model produced the best fit of the data. Their resultant calculated absolute risk for thyroid cancer in the entire exposed population of Nagasaki was 1.3 cases per million persons per rad per year. For women, the absolute risk was 1.9 cases per million persons per rad per year compared to a value of 0.65 cases per million persons per rad per year for men.

3.3 Lethality of External Radiation-Associated Thyroid Cancers

Mortality experience from radiation-associated thyroid carcinomas is limited. The 1977 UNSCEAR Report identified 4 deaths in 142

(about 3 percent) radiation-associated cases of thyroid cancer within a mean of 24 years after exposure. In the thymic-irradiated patients from Rochester, New York with thyroid cancer (Woodard, 1980), 2 of 28 cancers (about 7 percent) had been fatal over a mean period of 35 years since irradiation.

Compilations of clinical experience with external radiation-induced thyroid cancers suggest that, with rare exceptions, the tumors are of the well-differentiated adenocarcinoma variety. About 90 percent of these radiation-associated human thyroid carcinomas have been of the papillary type and about 10 percent have been of the follicular type, using World Health Organization criteria (Roudebush *et al.*, 1978) (Table 3.5).

Roudebush *et al.* (1978) also have compared the clinical outcomes of 91 patients with radiation-associated thyroid carcinomas to the outcomes of patients with similar carcinomas, but without a history of therapeutic irradiation in childhood. The patients with radiation-associated thyroid cancers had a higher incidence of multicentric disease, local invasion, distant metastases, and recurrences than those without a prior history of x irradiation and received more aggressive therapy. The mean follow-up times after surgery, 10.2 years in the irradiated group and 12.2 years in the non-irradiated group, were relatively short. Over this time span, there were no significant differences in mortality due to thyroid cancer in the two groups.

In a study of slightly more than 1100 patients with spontaneous thyroid adenocarcinoma, McConahey (1981) found that after 25 years, 5.7 percent of patients with papillary carcinoma of the thyroid had died of the disease and approximately 18 percent of those with follicular carcinoma had died of this disease (Table 3.5). Applying these mortality figures to the distribution of people with radiation-associated thyroid cancer would suggest that up to about 7 percent of patients with radiation-induced cancer will die of their disease over the first 25

TABLE 3.5—*Outcome from well-differentiated thyroid cancer*

Parameter	Papillary	Follicular	Reference
Histologic Classification of Radiation Associated Thyroid Cancers	90%	10%	Roudebush *et al.* (1978)
Observed 25-year Mortality due to Spontaneous Thyroid Cancer	5.7%	18%	McConahey (1981)
Composite mortality = $(90 \times 0.057) + (10 \times 0.18) = 6.9\%$[a]			

[a] Approximately ¾ of the deaths will be due to papillary cancer $[(90 \times 0.057) \div 6.9]$ and ¼ to follicular cancer $[(10 \times 0.18) \div 6.9]$

years after diagnosis. Projections for 1983 from the American Cancer Society (Silverberg *et al.*, 1983) suggest that the mortality rate for all thyroid cancer in the United States will be about 12.1 percent for males and about 9.6 percent for females, for an average of about 10.4 percent in a population composed equally of both sexes.

Numerous studies have shown a definite influence of age at diagnosis on mortality from thyroid cancer (Byar, 1979). These age-associated differences are not entirely related to an increased prevalence of poorly-differentiated, more highly lethal histologic types of cancer in the older age groups. The apparent benefits of youth at the time of diagnosis may explain why death rates in the people with thyroid cancer following irradiation in childhood have appeared somewhat lower than those projected for the general population. The lack of data from longer periods of observation of irradiated children who have developed thyroid cancer, and the lack of any indication that radiation-associated cancers are less aggressive than similar tumors in non-irradiated people, suggest that a projected lifetime mortality of 10 percent is a reasonable estimate for radiation protection purposes in a general population in whom the radiation-associated thyroid cancers would be diagnosed and treated only as they become clinically evident. Medical intervention in terms of early diagnosis due to careful prospective follow-up beginning soon after exposure and of early treatment of any suspected cancers might lower the mortality. The possible distribution over time of deaths due to radiation-associated thyroid cancers is discussed in Appendix B.

3.4 Modifying Factors in Radiation-Associated Thyroid Cancer

3.4.1 *Age at Exposure—Human and Animal Studies*

The external radiotherapy studies noted previously were of people irradiated in childhood or adolescence. No equivalent studies exist on thyroid cancer induction from similar therapeutic radiation exposures in adults. There are, however, several populations that have been exposed to other types of thyroidal irradiation; data from these groups can give some insight into the question of the influence of age on thyroid neoplasia.

Dobyns *et al.* (1974) reviewed the results of a follow-up study on 19,000 patients who received ^{131}I therapy for the treatment of Graves'

disease. Of these patients, a significant increase in thyroid adenomas was observed in the youngest quartile of the population (precise ages not stated). Radiation dose comparisons by age group are not available.

Prentice *et al.* (1982) (Table 3.4) have shown that the incidence of thyroid cancers in people exposed to radiation from the atomic bomb in Nagasaki at less than age 30 years is higher than the incidence in those greater than age 30 years at exposure. Parker *et al.* (1958–1971, 1974) suggested that people exposed to atomic bomb radiation when under the age of 20 years were at about twice the risk for thyroid cancer of those exposed later in life.

Following nuclear weapons testing in 1954, about 251 native persons living in the Marshall Islands were accidentally exposed to atomic fallout. Thyroid irradiation resulted from external gamma radiation, and from internally deposited short-lived nuclides of radioiodine (^{132}I, ^{133}I, ^{134}I, ^{135}I), ^{131}I, and radiotellurium (^{132}Te, ^{131m}Te). The people involved have been carefully observed for adverse health effects, including thyroid cancer. A 26-year follow-up report has been published (Conard, 1980), and thyroid dose estimates have been re-evaluated (Lessard *et al.*, 1983). Radiation exposures to the thyroids of those less than 18 years of age were greater (1130 rads) than those of the older groups (470 rads) (Lessard, 1983). The higher radiation doses to the younger subjects reflected their smaller thyroid gland sizes as well as differences in inhalation and ingestion pathways in the various groups. When thyroid cancer induction was examined, no definite age differences were found although the expression of radiation carcinogenesis may have been altered by the administration of thyroid hormone to some of the exposed subjects as well as by intervening surgery for the removal of benign thyroid nodules. A total of 7 thyroid cancers was reported initially (Conard, 1980) but one of these has been re-categorized as benign (Lessard, 1983). The prevalence of excess thyroid cancers in the group under the age of 10 years (including in utero) at exposure was about 2.2 percent, compared to about 3.3 percent in the 10- to 18-year old group; and to about 2.3 percent in the subjects over the age of 18 years (Lessard, 1983).

The possibility of increased effects of radiation (radiosensitivity) on young (infants, children, and adolescents) thyroid glands over that of mature (adult) glands is complicated by the increased concentrations of radioiodines in smaller thyroid glands following inhalation or ingestion by children and by differences in iodine metabolism in children, as compared with adults who may take in the same quantity of radioactive material. After reviewing the limited animal and human data, Book (1978) suggested that radiation doses to the thyroid from

inhalation of fixed concentrations of environmental radioiodine in air were twice as great in infants as in adults, and up to 10 times the adult value in the near-term fetus. For comparison, by the ingestion route, the 6-month-old infants were considered likely to receive over 30 times more thyroidal radiation dose than the adults, the difference being primarily due to the smaller gland size and the ingestion of larger quantities of contaminated milk.

An increase in radiosensitivity implies that more effects result from the same radiation dose. A possible increase in radiosensitivity in the young thyroid has been observed in animal studies of non-malignant thyroidal effects of irradiation.

Sikov (1969) investigated the influence of age in rats on the ability of an ^{131}I-exposed thyroid to concentrate tracer levels of ^{131}I at 4 months after the initial exposure. The differences in dose required to suppress tracer uptakes to 50 percent of the control value suggested that fetal thyroids were nearly 20 times more radiosensitive for functional damage than those in adults. Comparable results in neonates and weanlings yielded sensitivities about 3 and 1.5 times, respectively, as compared to adults. Book *et al.* (1980b) examined thyroid effects of ^{131}I uptake as a function of age at exposure in guinea pigs exposed to single graded administrations. Using the reduction of thyroidal tracer ^{131}I uptake at 100 days post-exposure as the criterion for radiosensitivity, they concluded that the thyroids in fetuses and weanlings were about 2 times as radiosensitive as those in adults and 4 times as sensitive as those in newborns. These studies considered functional parameters and were not designed to look at carcinogenesis.

A study that was concerned with neoplasms and utilized external irradiation to address the question of age-related sensitivity of thyroid glands was done by Christov (1978). In that experiment, Wistar rats were exposed to x rays with an absorbed dose of 300 rads to the neck; 15 months later their thyroids were examined for tumors. Forty percent of the animals irradiated at 10 days of age had thyroid tumors (all adenomas), while 15 percent of those irradiated at 60 days of age had these tumors. No tumors were evident in controls. In animals treated with a goitrogen after irradiation, 96 percent and 72 percent of the younger and older animals, respectively, had thyroid tumors. Of the total tumors in the irradiated, goitrogen-treated animals, 13 percent were carcinomas in the 10-day group, and 7 percent were carcinomas in the 60-day group. Among unirradiated, goitrogen-treated animals, 70 percent of the 10-day animals had thyroid tumors (no carcinomas) and 48 percent of the 60-day animals had thyroid tumors (7 percent of the total tumors were carcinomas).

These limited data from epidemiological and laboratory studies indicate that age at exposure is a modifying factor for thyroid carcinogenesis because of increased radiosensitivity of the thyroids of young animals and children. The animal data suggest about a 2-fold increase in susceptibility to radiation-carcinogenesis for thyroid glands in the young as do the Japanese human data.

Possible influences of promoting or modifying factors other than radiosensitivity that might also contribute to this apparent age-related susceptibility are not defined.

3.4.2 *Sex*

The studies on subjects exposed to external radiotherapy in childhood suggest that females show a greater clinical effect in terms of radiation carcinogenesis of the thyroid than men exposed under similar conditions (Sampson *et al.*, 1970). In the University of Rochester studies (Hemplemann *et al.*, 1975), females had 2.3 times the incidence of males, while in the University of Cincinnati studies (Maxon *et al.*, 1980), the ratio was 2.2. In the Israeli population irradiated for *Tinea capitis* (Ron *et al.*, 1984), the excess risk for thyroid cancer in women was about 4 times that for men. Shore (1980) has demonstrated that the absolute risk of thyroid cancer following thymic irradiation in childhood is significantly higher in women than in men (about 2.9 times greater in women). In the Marshall Islands' subjects (Conard *et al.*, 1980) all 7 cancers occurred in women. In the Japanese A-bomb survivors (Parker *et al.*, 1958–1971, 1974), the incidence of thyroid cancers in females exceeded that in males in every exposure group with an overall female/male ratio of about 2.7, and the absolute risk in women is 2.9 times that in men (Wakabayashi *et al.*, 1983). Based on estimates from the SEER (Surveillance, Epidemiology, and End Results) program of the National Cancer Institute (Silverberg *et al.*, 1983) the female/male risk ratio for thyroid cancer in the general population of the U.S. is 2.5.

These data are consistent with an increased absolute risk coefficient for radiation-induced clinical thyroid cancer in females, which is about 2 to 3 times that for males exposed under similar conditions.

3.4.3 *Ethnic Background*

There are some data that suggest that ethnic background influences risk of radiation induced thyroid cancer. The Rochester study (Hemplemann *et al.*, 1975) of 2872 people irradiated in childhood shows that

a disproportionate number of cancers (11 of 24 or 46 percent) were found in the 8 percent of the population that is Jewish. This same Jewish population contributed 23 percent of the total person-rad-years in the study. Nevertheless, the relative risk for Jews compared to non-Jews was about 3.5 after adjusting for sex, time since irradiation, and radiation dose (Shore, 1980). When the Jewish subjects are excluded, the absolute risk of thyroid cancer becomes about 2 cases per million persons per rad per year, which is close to the value of 1.8 cases per million persons per rad per year found in the predominantly non-Jewish Cincinnati study (Maxon *et al.*, 1980). Higher risk estimates were obtained in the Israeli *tinea capitis* study (Ron *et al.*, 1984) (risk about 14 per 10^6 per rad per year) and Michael Reese study (Frohmann, *et al.*, 1977) (risk about 2.6 per 10^6 per rad per year), both of which involve predominantly Jewish populations. The reasons for these differences may be related to ethnic background, particularly in light of the absence of cases in similarly (to the Israeli study) irradiated patients in the New York *tinea capitis* study which was comprised of 89 percent non-Jewish and 24 percent black subjects (Shore *et al.*, 1976), although the absence of cases of thyroid cancer in the New York population is not statistically incompatible with the Israeli experience. In the Israeli study, the absolute risk of thyroid cancers in the subjects emigrating from Morocco or Tunisia was about twice that for subjects emigrating from other areas (Ron *et al.*, 1984), although the differences were not statistically significant due, in part, to the small number of spontaneous cases in non-irradiated cohorts.

It also has been observed that the prevalence of incidentally-noted thyroid cancer at autopsies performed on the general population may be about 3 to 6 times higher in Japan than in the United States (Sampson *et al.*, 1969; Fukunaga *et al.*, 1971) whereas the incidence of clinical thyroid cancer is lower in Japan. Within the United States, the incidence of thyroid cancer varies considerably by ethnic group, with black Americans having only about 2/3 the incidence of white Americans. Chinese, Filipino, or Hawaiian women living in Hawaii have about twice the incidence of thyroid cancer as white women living in Hawaii (Table 3.6). Thyroid cancer incidences from tumor registries in various parts of the United States and the world are shown in Table 3.6.

3.4.4 *Heritage*

From the collective body of human and animal data regarding radiation related thyroidal carcinogenesis, it appears that radiation represents an initiating factor for thyroid cancer that is superimposed

TABLE 3.6—*Thyroid cancer incidence for each registry–number of cases (both sexes) and age standardized rates per 100,000 persons*[a]

Geographical Area	Total No. of Thyroid Cancers	Age Standard Rates/100,000	
		Male	Female
United States			
Alameda: White	133	3.2	6.4
Black	8	1.9	2.7
Bay Area: White	459	3.4	7.3
Black	21	2.5	3.5
Chinese	18	2.6	9.4
Connecticut	321	1.9	4.4
Iowa	170	1.8	4.2
Detroit: White	293	2.3	6.2
Black	37	1.3	4.1
N. Mexico: Spanish	32	2.6	5.9
Other White	62	2.9	6.3
Amer. Indian	6	3.1	6.3
New York State	509	1.4	3.5
El Paso: Spanish	11	3.3	6.6
Other White	11	0.4	4.9
Puerto Rico	158	0.8	3.1
Utah	124	2.3	5.8
Hawaii: Hawaiian	6	4.9	19.1
Caucasian	53	3.7	10.9
Chinese	16	5.1	17.2
Filipino	22	6.9	24.0
Japanese	44	4.4	9.5
Other Countries			
Nigeria	26	1.0	2.3
Canada	890	1.5	4.0
Israel: Jewish Only			
Born Israel	65	6.3	7.2
Born Eur./Amer.	217	5.2	8.2
Born Afr./Asia	139	3.0	7.6
Sweden	921	1.9	4.3
Japan	260	0.7	2.8

[a] Age-standardized rates based on Waterhouse *et al.* (1976).

on other factors such as species, genetic background, ethnic groups, environment, etc. (collectively referred to as "heritage"), age, and sex. This indicates the importance of deriving risk estimates from populations that are as similar as possible to those to which the risk estimates are to be applied. However, adequate information often does not exist for such calculations. Assuming that differences between age- and sex-adjusted thyroid cancer rates for specific populations at least partially reflect differences in the heritage of those populations, a comparison of the incidence rates may provide an estimate of the

TABLE 3.7—*Thyroid cancer incidence rates (age standardized to the European population)*[a]

Population	Males		Females	
	Rate	Normalized[b]	Rate	Normalized[b]
Continental United States, White	2.3	0.43	5.4	1.00
Continental United States, Black	1.8	0.34	3.4	0.63
Canada	1.5	0.27	4.0	0.75
Israel, Jews born in Europe or North America[c]	5.2	0.96	8.2	1.52
Sweden	1.9	0.35	4.3	0.80
Japan	0.7	0.13	2.8	0.52

[a] Cases/100,000 persons based on Waterhouse *et al.* (1976) (Table 3.6)

[b] Geometric mean normalized to white females in the United States

[c] Jews born in Europe or America were not included in the irradiated populations studied by Ron and Modan (1984)

magnitude of the problem of different heritages in determining incidence rates (Table 3.7). If the normalized, age-adjusted incidence factors (Table 3.7) are applied to the approximate ethnic composition of the population of children irradiated in the United States from whom the risk estimate for external radiation in childhood was derived (Table 3.2), then the resultant proportional incidence is identical to that which would be predicted for a non-Jewish, Caucasian population comprised equally of both sexes (72 percent of projected incidence for non-Jewish, white women). For applications within the continental United States, the risk estimates derived from the studies of externally irradiated children given in Table 3.1 would appear to be applicable to a non-Jewish, Caucasian population comprised equally of both sexes and might overestimate the risk in black Americans while underestimating the risk in Jewish Americans.

4. Human Experience after Exposure to Iodine-131

4.1 Therapeutic ^{131}I for Thyrotoxicosis

4.1.1 *Adults*

Dobyns *et al.* (1974) found that 86 of 16,042 patients with Graves' disease without palpable nodules at the time of radioiodine therapy were subsequently operated on and found to have nodules after ^{131}I therapy. Approximately 98 percent of the 16,042 patients were over the age of 20 years at the time of treatment. The mean followup time was only 8 years. Two of these 86 patients were operated on because of recurrent thyrotoxicosis, but in both of these a palpable mass was specifically described in the thyroid. In the other 84, surgery was presumably indicated because of some palpable abnormality (Tompkins, 1976). Nine of the 86 (10.5 percent) had cancer and 77 (89.5 percent) had benign lesions. In an additional 494 of 16,042 patients, palpable nodules were found to have developed after ^{131}I therapy, but the 494 had not undergone surgery and have not been systematically followed since the end of the study. Based on the 9 documented cases of thyroid cancer, the prevalence of thyroid cancer would be about 0.06 percent in radioiodine treated patients, compared to a spontaneous prevalence in Graves' disease of about 0.1 percent. On the assumption that the prevalence of cancer would be the same in 494 unoperated patients as in the 86 patients subjected to surgery, 52 additional cases of thyroid cancer could be postulated. These assumptions would suggest a maximum prevalence of thyroid cancer of about 0.4 percent in ^{131}I treated patients. The radiation dose in these patients was always more than 2000 rads, with a mean of approximately 8755 rads to the thyroid, based on an assumption of a 6-day effective half-life (Maxon *et al.*, 1977; O'Connor *et al.*, 1979).

Holm and associates reported on 4557 people with hyperthyroidism who were treated with ^{131}I in Sweden (Holm *et al.*, 1980b; Holm, 1984). The mean follow-up period was 9.5 years and the mean age of the subjects was 56 years at the time of exposure. The mean administered

activity of ^{131}I was 13 mCi, calculated to deliver between 6000 and 10,000 rads in most cases. The subjects were about equally divided between those who had toxic diffuse goiters and those who had toxic nodular goiters. A total of 4 thyroid cancers was found, and all were in women with previous toxic nodular goiters treated with a mean total activity of 27.5 mCi ^{131}I. Based on Swedish tumor registry data from non-irradiated women with nodular goiters, 2 cases were predicted. The difference between 2 expected and 4 observed cancers was not considered significant. In a separate population, Sokal (1954) estimated the prevalence of thyroid cancer in toxic nodular goiter to be 0.94 percent. Application of this figure to the approximately 1900 women with toxic nodular goiter in the Holm study (Holm, 1984) results in a prediction of about 18 spontaneous cancers.

In the two populations discussed above (Dobyns *et al.*, 1974; Holm, 1984) with a total of 20,599 adult subjects followed for means of 8 and 9.5 years, there is no evidence of ^{131}I-induced thyroid carcinogenesis at high dose levels (greater than 2000 rads) in adults. This apparent absence of carcinomas may be due in large part to the effects of cell-killing and/or sterilization at such high dose levels and/or to the short follow-up times in relatively (compared to children) radioresistant adults.

4.1.2 *Children*

Safa *et al.* (1975) have reported on 273 patients treated between the ages of 1 and 20 years with ^{131}I for Graves' disease. There were 31 additional children aged 16 years or less who were treated with ^{131}I in the Cooperative Thyrotoxicosis Follow-up Study (Tompkins, 1976). Pooling of these observations reveals 2 cases of thyroid cancer in the combined population of 304 people followed after ^{131}I therapy. Estimates of mean thyroid dose and follow-up period, available from 271 of 304 subjects, are about 9,000 rads and about 11 years. The 2 observed cancer cases are more than might be expected spontaneously in Graves' disease (0.3 case), although the difference between the observed and expected cases is not considered significant.

4.2 Non-therapeutic Exposures to ^{131}I

Holm *et al* (1980a, 1981) reported a retrospective analysis of outcome in 10,133 subjects exposed to diagnostic administration of ^{131}I (total

less than 1 mCi) for suspected thyroid disease. The population included 8047 females (79 percent) and 2086 males (21 percent) with a mean age of 44 years for both sexes. Of the 10,133 subjects, 9639 were over the age of 20 years at exposure and 494 were less than 20 years of age. For the 9639 adults, the mean calculated thyroidal dose was 58 rads, whereas, in the 494 younger subjects, the mean dose was 159 rads. Patients were followed for a mean time (after adjustment for drop-out due to death), of 17 years after exposure to ^{131}I. No patients were included who had received external radiation therapy above the diaphragm or who had been treated previously with other internal emitters. Any cancers diagnosed less than 5 years after the ^{131}I exposure were excluded as not being related to the exposure. The study had insufficient data to take into account possible effects of intervening thyroid hormonal or surgical therapy after the radioiodine exposure on the subsequent development of thyroid cancer. In 8 patients, a thyroid cancer was confirmed as being present. All 8 of the cancers were in the 9639 adults; none was found in the children. Six of the 8 cancers (75 percent) occurred in women and 2 (25 percent) in men, reflecting the sex ratio of the study population as a whole. This did not represent any significant increase in cancer in the irradiated population. The expected number of thyroid malignancies, computed from age- and sex-specific cancer incidences in the Swedish Cancer Registry, was 8.3 cases over the period at risk (follow-up time minus 5 years).

Since 1973, a national collaborative study of children exposed to diagnostic levels of ^{131}I between 1946 and 1967 has been in progress under the auspices of the Bureau of Radiological Health of the U.S. Department of Health and Human Services, with support from the National Cancer Institute and the Nuclear Regulatory Commission. The study was designed to include about 13,000 potential subjects, equally divided among controls, exposed persons, and siblings of irradiated people (Harris, 1980). No data have been made available since preliminary communications regarding 443 of the subjects in 1975 (Hamilton *et al.*, 1975). Those communications suggested that at mean doses of 94 rads to the thyroid, with a range of less than 10 to 1900 rads, 6 subjects of 443 who received diagnostic ^{131}I studies in childhood were found to have benign thyroid nodules, and none of the 443 was found to have thyroid cancer at least 16 years later. There was no significant correlation between estimated thyroidal radiation dose and the incidence of benign nodules.

In a survey of 5179 children, of whom 1378 had been exposed to ^{131}I in radioactive fallout in the western United States, Rallison *et al.*

(1974) could find no significant differences between irradiated and non-irradiated subjects in the prevalence of thyroid nodules, benign and malignant, at an average follow-up time of 14 years. The dosimetry is uncertain and undergoing extensive review, but new dose calculations are not yet available. The lowest figure proposed has been a mean thyroidal dose of 18 rads (Rallison *et al.*, 1974) with some other estimates being an order of magnitude higher (BEIR, 1980). Because of the uncertain dosimetry these data have not been used for risk estimates in this report.

For children exposed to diagnostic ^{131}I, the combined studies represent a total of 937 subjects representing 1.4 million person-rad-years at risk. For adults, the Swedish study contains 9639 subjects representing about 6.7 million person-rad-years at risk. If the absolute risk estimates derived earlier from carcinogenesis following external radiation exposures in childhood in the United States were applicable to these populations exposed to ^{131}I, then an excess of about 3–4 thyroid cancers in children and of about 8 to 9 thyroid cancers in adults would be expected, assuming that adults are at about one-half the risk of children. However, these experiences, with mean thyroidal doses from ^{131}I which are well below 200 rads, contain no evidence for the presence of human thyroidal radiation carcinogenesis.

4.3 The Relative Carcinogenicity of ^{131}I and External Radiation

Because ^{131}I has not been shown to be carcinogenic in people, a comparison of the thyroid cancer risk from ^{131}I with that from x-ray exposure is difficult.

Hanley *et al.* (1983) have discussed the problem of interpreting zero numerators. To find the largest number of excess cases with which a finding of 0/n is still compatible with the data at the upper bound of the 95% confidence level, one may solve the equation:

$$\text{Largest Number of Excess Cases} = 1 - (0.05)^{1/n} \qquad (4\text{-}1)$$

In the case of 937 children exposed to relatively low doses from diagnostic ^{131}I, this calculation results in a value of 0.00319 or about 3.2 excess cases/1000 as the upper 95 percent limit of risk compatible with zero observed cases. If the observed risk of 2.5 excess cases/10^6 person-rad-years at risk following external irradiation in childhood

were applicable, then with 1.4 million person-rad-years at risk one would expect 3.5 cases/937 or about 3.7 cases/1000. For the 9639 adults exposed to diagnostic ^{131}I, similar calculations using a risk following external irradiation of 1.25 excess cases/10^6 person-rad-years at risk (i.e., adults = one-half the risk of children) lead one to expect 0.87 excess cases/1000. The largest number of excess cases compatible with the upper 95 percent limit of a zero numerator in the adults is 0.31 cases/1000. Therefore, since the risk estimate derived for external radiation predicts a larger number of excess cancer cases than the upper 95 percent limit for what was observed in the ^{131}I exposed patients, then the risk of human thyroidal carcinogenesis following exposure to ^{131}I would appear to be less than the risk following exposure to the same dose from external x radiation.

Another approach to the question of the relative carcinogenicity of ^{131}I and external radiation needs to be considered. Choi (1978) and Feinstein (1977) have discussed mathematical models for predicting the minimum number of subjects required in a study of adverse effects characterized by an increased incidence of a spontaneously occurring abnormality. The number of subjects may be given by the formula:

$$n = \frac{Z_\alpha{}^2 \cdot P_0 \cdot (1-P_0)}{(P-P_0)^2}, \tag{4-2}$$

Where Z_α is the standard normal (Gaussian) variate at a specified level of significance, α, which is 1.645 for a single tailed test at $\alpha = 0.05$; P_0 is the proportion of cases in which thyroid cancer occurs naturally; and P is the proportion of cases in which thyroid cancer occurs after radiation, including spontaneous cases. Implicit in this formula is the assumption of a power of 50% (or $\beta = 0.5$ and $Z_\beta = 0$) in order to approximate a central estimate analogous to the risk estimate calculation for external radiation. $P-P_0$ can be defined by the risk estimate (in cases per million per rad per year) [see Eq. (2-1)] times the number of person-rad-years at risk times 10^{-6}, divided by the number of persons in the population. One may then modify the basic equation to give the risk level at which one would expect to find an excess number of radiation-associated thyroid cancers in a given exposed population at $\alpha = 0.05$ as follows:

$$\text{Risk} = \frac{n \cdot 10^6}{\text{person-rad-years at risk}} \sqrt{\frac{(1.645)^2 (P_0)(1 - P_0)}{n}}. \tag{4-3}$$

In applying Eq. (4-3) to the human data following low dose ^{131}I exposures, it would appear that if external radiation and ^{131}I are equally harmful in terms of thyroid cancer induction on a rad-for-rad basis,

then for the population of 9639 people exposed in adult life in Sweden and representing 6.7 million person-rad-years at risk with a spontaneous thyroid cancer rate in the unexposed Swedish population of 8.3/10,133 or $8.19 \cdot 10^{-4}$, and for a population of 937 people exposed in childhood and representing 1.4 million person-rad-years with an estimated spontaneous rate of clinically detectable thyroid cancer of about $3 \cdot 10^{-4}$, at $\alpha = 0.05$, one should find an excess of radiation-associated thyroid cancers at risk levels of greater than 0.62 to 0.69 cases per million person per rad per year for children and adults respectively.

In other words, if the risk following ^{131}I exposure is equal to or greater than 0.6 to 0.7 cases per million persons per rad per year, then one should be able to detect the excess cancers at $\alpha = 0.05$. In fact, no excess cancers were determined to be present. The calculation in the case of children is less certain due to the small numbers and lack of precise information regarding their actual spontaneous rate of thyroid cancer as they reach adult life.

Thus, in summary, ^{131}I appears less carcinogenic in people on a rad-for-rad basis than external radiation. How much less is yet to be determined; in fact, available human data on low dose ^{131}I exposures have not shown ^{131}I to be carcinogenic in the human thyroid. A comparison for children of the risk coefficient for ^{131}I of 0.6 cases per million persons per rad per year to the risk of thyroid cancer of 2.5 cases per million persons per rad per year following external radiation suggests that ^{131}I is no more than about one-fourth as effective as external radiation. For adults, a similar calculation using 0.7 cases per million persons per rad per year for ^{131}I and a risk of 1.25 cases per million persons per rad per year following external radiation, suggests that ^{131}I is no more than one-half as carcinogenic as external radiation.

Based on human experience, the range of the relative effectiveness of ^{131}I compared to external radiation is between zero and one-half. Combining the calculated values in children (¼) and adults (½) for application to the general population, an upper limit value of one-third is recommended for application to the general population, until additional data become available.

5. Animal Data Relating ^{131}I to External Radiation Exposure in the Induction of Thyroid Neoplasms

The carcinogenic potential of ^{131}I relative to external exposure has been studied only to a very limited extent. After the early reports of ^{131}I-induced thyroid cancers in hooded Lister rats (Doniach, 1950) and Long-Evans rats (Goldberg and Chaikoff, 1951), other studies in rats also demonstrated ^{131}I-induced tumorigenesis. Many of these investigations utilized Long-Evans rats, which developed thyroid carcinomas as well as adenomas from ^{131}I exposure (Goldberg and Chaikoff, 1952; Lindsay *et al.*, 1957, 1963; Potter *et al.*, 1960; Goldberg *et al.*, 1964). In hooded Lister rats, adenomas were produced by ^{131}I, but carcinomas appeared only after the addition of post-irradiation goitrogenic stimulation (Doniach, 1950, 1953, 1957). A single adenoma was observed (out of an undisclosed number) in Sprague Dawley rats given ^{131}I (Maloof *et al.*, 1952). Thyroid tumors unclassified as adenomas or carcinomas were also reported in rats of the BN/Bi strain (de Ruiter *et al.*, 1976).

Doniach (1957) found thyroid adenomas (and adenomas and carcinomas when goitrogen-stimulated) in hooded Lister rats following 1100 rads of x-irradiation or 30 μCi of ^{131}I (estimated by Doniach to give between 2000 and 24,000 rads), representing a range of effectiveness for ^{131}I of one-half to one-twentieth of that of x-irradiation. In Long-Evans rats exposures to 25 μCi of ^{131}I (Lindsay *et al.*, 1957) and, in a later experiment, 1000 R from x rays (Lindsay *et al.*, 1961) gave comparable thyroid adenoma and carcinoma production. Doniach (1963) reviewed these studies and concluded that ^{131}I was one-tenth as effective as external irradiation for producing radiobiologic effects on the thyroid.

Walinder (1972) studied the comparative carcinogenesis of x-irradiation and ^{131}I in adult CBA mice. His results indicate that ^{131}I was one-fourth to one-tenth as effective as x-irradiation in the production of thyroid adenomas and carcinomas. The range of effectiveness is

based on exposures of 1500 R from x ray vs 6400 to 16,000 rads from ^{131}I (considering the difference in dose to the thyroid lobe's periphery and its center). His results also indicate that, at slightly lower doses, the relative effectiveness of ^{131}I was one-half to one-tenth, based on an exposure of 1000 R from x rays and a dose of 2200 to 11,000 rads from ^{131}I. Walinder also mentioned in the same report that ^{131}I had been observed to produce malignant thyroid tumors only in his CBA mice and in the Long-Evans rat (see above), recalling that Doniach's hooded Lister rats required subsequent goitrogenic challenge to produce thyroid carcinomas.

More recently, in a large study with 3000 Long-Evans rats, Lee *et al.* (1982) examined the thyroids 2 years after an exposure at 6 weeks of age to 80, 330, or 850 rads to the thyroid from 0.48, 1.9, or 5.4 μCi of ^{131}I, respectively, or to 94, 410, or 1060 rads from localized x irradiation. The doses from ^{131}I in this study were considerably lower than those in the earlier studies. Exposure to ^{131}I was found to be about 40 percent as effective as x-irradiation at the highest exposure for the production of adenomas, and about the same as x-ray at the lower exposures. For the production of thyroid carcinomas, the two radiation types appeared to be of equal effectiveness at all three doses although the results did not preclude a relative effectiveness of ^{131}I of as little as one-third compared to external radiation.

The differences in effectiveness observed in the study of Lee *et al.* (1982) and the earlier rat studies may reflect differences in age at exposure (those in the more recent study were generally 2 to 6 weeks younger), and for Doniach's work, the strain of rat used. Lee *et al.* (1982) considered the differences to result from the earlier studies' poor animal survival, small sample size, excessively high doses, and differences in observation periods and sex of the animals. The differences in the relative effectiveness observed in rats by Lee *et al.* (1982) and in mice by Walinder (1972) may be related to species differences, differences in age, or to the high doses, particularly from ^{131}I, that were used in the latter study.

The results of Lee *et al.* (1982) provide the largest single body of thyroid cancers induced by ^{131}I or x irradiation in an animal model. Their dose range was low and in the realm of concern to those who must assess risks from low-level radiation exposures. Their study, however, with termination 2 years after exposure, apparently followed a standard experimental design for determining whether a test material is carcinogenic, rather than one for determining lifetime risks and dose-effect relationships. The latter, under ideal conditions, could have allowed the animals to complete their life spans and might have

TABLE 5.1—*Summary of animal studies on the effectiveness of ^{131}I relative to x-irradiation or to short-lived radioiodines*

Author (Date)	Species	Effect	Effectiveness of ^{131}I[a]	Dose, Exposure, or Administrated Activity		
				X ray	^{131}I	Other
Tumorigenesis						
Doniach (1957)	Rat	Thyroid adenomas, cancers	1/2–1/20	1100 rads	30 μCi, est. by Doniach to give 2000–24,000 rads	
Lindsay *et al.* (1957)	Rat	Thyroid adenomas, cancers	1/5	1000 R	25 μCi (~5000 rads, estimated)	
Lindsay *et al.* (1961)	Rat	Thyroid adenomas, cancers				
Doniach (1963)		Review of above	1/10			
Walinder (1972)	Mouse	Thyroid adenomas, cancers	1/4–1/11	1500 R	6400–16,000 rads	
Walinder (1972)	Mouse	Thyroid adenomas, cancers	1/2–1/11	1000 R	2200–11,000 rads	
Lee *et al.* (1982)	Rat	Thyroid adenomas, carcinomas	1/1–1/2.5 for adenomas; 1/1 for carcinomas	94–1060 rads	80–850 rads	
Other Effects						
McClellan *et al.* (1963)	Sheep	Histologic changes	1/20	750–3000 R	24,000–90,000 rads	
Greig *et al.* (1970)	Rat	Inhibition of goitrogenesis	1/5 at low doses; 1/15–1/30 at high doses	100–1800 rads	530–51,000 rads	

Klassovskii *et al.* (1970)	Rat and Dog	Histologic, functional changes	1/10–1/25		Hundreds to tens of thousands of rads	Hundreds to tens of thousands of rads from a mixture of 10% I-131 and about 90% I-132, I-133, I-135
Walinder & Sjoden (1971)	Mouse	Inhibition of goitrogenesis	1/2–1/4	1500 rads	1000–14,000 rads	
Walinder & Sjoden (1972)	Mouse	Thyroid gland growth	1/5–1/10	180 rads	1500–2000 rads	
Walinder *et al.* (1972)	Mouse	Inhibition of goitrogenesis	Not stated but suggests x-ray and I-132 about the same	1000–1500 rads	4000–5000 rads	1200–2400 rads from I-132
Book *et al.* (1980a)	Rat	Inhibiton of goitrogenesis	1/9		60–16,000 rads	1–800 rads from I-132

[a] Relative to x ray or other iodine isotopes

shown differences in latency rather than incidence. This is important, for some additional cancers may have appeared after the end of the 2-year study, since roughly two-thirds of the animals remained alive. It is known that at tumorigenic doses, other non-thyroidal types of tumors tend to appear later with low doses than with high doses, as shown in studies with x irradiation in mice (Upton *et al.*, 1960; Upton, 1961) and dogs (Andersen and Rosenblatt, 1969), and with bone-seeking radionuclides in mice (Brues, 1949; Finkel, 1953) and dogs (Mays *et al.*, 1969; Raabe *et al.*, 1981). Therefore, if thyroid tumors behave like other tumors in terms of increased induction time with lower doses, more thyroid tumors would have been seen after the two-year period, and the resultant risk estimates would have increased to some extent.

The information from laboratory animals on the comparative aspects (x rays vs. ^{131}I) of radiation-induced thyroid carcinogenesis at low doses is relatively limited. Additional data from other rodent strains and other species would be desirable. In addition, the influence of time on the dose-effect relationship, not only very late in life, as discussed above, but also early on, with regard to whether or not latency is dose-related, needs to be addressed. Extrapolation from animal data to humans remains a difficult process of uncertain validity.

5.1 Significance of the Animal Data

As demonstrated in several studies (Table 5.1), data at high exposures in Long-Evans rats (Lindsay *et al.*, 1957, 1961) and CBA mice (Walinder, 1972) suggest that ^{131}I is about one-tenth as effective as external radiation for the production of thyroid cancers, as do data from goitrogen-stimulated hooded Lister rats (Doniach, 1957). Adenoma production in the latter strain also suggests a factor of about one-tenth.

At lower doses (~100 to 1000 rads) and dose rates, the effects in Long-Evans rats (Lee *et al.*, 1982) showed that ^{131}I and x-irradiation each produced thyroid neoplasia. Iodine-131 had about the same effectiveness as x rays for the production of carcinomas at all exposures, although a relative effectiveness factor of one-third could not be excluded. For adenomas, ^{131}I was about 40 percent as effective as x rays at about 1000 rads, but of about the same effectiveness at lower doses.

The combined animal data suggest that the relative effectiveness of

^{131}I compared to x-irradiation may be lower at high doses and dose rates, and higher (that is, nearer to x ray in effectiveness) at low doses and dose rates. That two radiation modalities may have a varying relative effectiveness over a range of exposures is suggested by the results of Lee *et al.* (1982) for adenomas, and was mentioned by Walinder (undated publication).

None of the animal data preclude an estimated maximal relative effectiveness factor for thyroidal carcinogenesis following ^{131}I exposure of one-third as compared to external radiation. Given the possible species- and strain-dependent nature of the animal studies and the many uncertainties in the animal data, risk estimates in this report will be based on human experience.

6. Experience with Iodine-125

Iodine-125 is used extensively in radioassay techniques for both research and clinical purposes. It has also been used occasionally in the past for treatment of hyperthyroid states.

Thyroid cancer following human thyroidal exposure to large amounts of ^{125}I has not been reported. This may reflect, in part, the small numbers of such subjects available for study and short follow-up times. Therefore, it is necessary to look at results from animal studies and at non-malignant effects in man.

The effects of ^{125}I have been investigated in a number of animal experiments. Most of these studies compared the effects on the thyroid of ^{125}I and ^{131}I.

Gross *et al.* (1967) studied young rats given large activities of either ^{125}I or ^{131}I and measured their ^{131}I uptakes periodically up to 11 months after the initial irradiation. Rats that received 100 or 500 μCi of ^{131}I or 500 μCi of ^{125}I had radioiodine uptakes that were suppressed to about one-tenth of the control value; those rats that received 100 μCi of ^{125}I had uptakes that returned to control values after 200 days. All four treatments markedly reduced the rats' growth in terms of body weight increase. These same authors found thyroid tumors in rats given 25 μCi of ^{125}I (2 out of 23), but not in rats given 25 μCi of ^{131}I (0/18), although the differences were not statistically significant. They also found no tumors in 55 rats given 300 μCi of ^{131}I, but only 14 survived the 502 day experimental period. Calculated thyroidal doses for the groups in the tumor study were 2400 rads for ^{125}I, and 14,000 and 29,000 rads, for the two ^{131}I groups, respectively.

Vickery and Williams (1971) used the inhibition of thyroidal goitrogenesis as a test for comparing the effects of ^{125}I and ^{131}I. For rats on a normal diet, 20 and 50 μCi of ^{125}I gave approximately the same results as 5 μCi of ^{131}I, and 300 μCi of ^{125}I gave the same effect as 20 μCi of ^{131}I. Rats on a low-iodine diet showed similar effects at 300 μCi of ^{125}I and 5 μCi of ^{131}I, the greater disparity being related to the increased follicular cell height caused by iodine deficiency with a consequent greater sparing of nuclei from irradiation from ^{125}I.

Greig *et al.* (1970) used the inhibition of goitrogenesis to compare ^{125}I, ^{131}I, and x irradiation. Doses to reduce the thyroid weight to about half the control value were 9300, 4200, and 500 rads for the three

irradiations respectively. For the iodine isotopes, the dosages corresponded to about 80 μCi of ^{125}I and 10 μCi of ^{131}I.

A study of the relative effects of ^{125}I and ^{131}I in rat thyroids (de Ruiter *et al.*, 1976), indicated that 32 to 80 μCi of ^{125}I gave effects comparable to those from 3.2 μCi of ^{131}I in terms of survival and thyroid function tests. For follicular cell hyperplasia, cysts, and tumors, 80 μCi of ^{125}I and 3.2 μCi of ^{131}I were comparable.

For all the above effects, from 6 to 60 times the activity of ^{125}I was required to yield the same effects as a given activity of ^{131}I. The ^{125}I doses per unit of administered activity were 3 to 6 times lower than those calculated for ^{131}I (Gross *et al.*, 1967; Greig *et al.*, 1970; Vickery and Williams, 1971). Hence, the relative effectiveness of ^{131}I compared to ^{125}I in rats is in a range of 1 to 20 for the same effects. The difference may be related to dose rate, dose distribution, and/or LET of the radiation (Malone, 1975).

Several investigators performed microdosimetric calculations that suggested the radiation dose from ^{125}I to the follicular cell/colloid interface, where iodination occurs, was greater than the dose to the nucleus (Gillespie *et al.*, 1970; Greig *et al.*, 1970; Vickery and Williams, 1971; Lewitus *et al.*, 1971; Gavron and Feige, 1972; van Best, 1981). These calculations followed the work of Gross *et al.* (1967), cited above, which also presented data on the goitrogenic response of thyroids of rats given relatively small activities of ^{125}I and ^{131}I. Iodine-125 was shown to have a greater effect than ^{131}I on hormonogenic aspects of the thyroid-pituitary axis, in that ^{125}I-treated animals were more responsive to goitrogens than ^{131}I-treated animals and controls, and pituitary glands of ^{125}I-treated animals were larger than those of the other groups.

Concern has been noted about the increase in thyroid stimulating hormone (TSH) from decreased hormonogenesis, which would then stimulate mitosis in those cells still able to respond. Such a condition would be favorable for the development of thyroid tumors (Lewitus *et al.*, 1971; Malone, 1975).

The appearance of hypothyroidism following exposure to ^{125}I has been evaluated in two major trials in man (McDougall *et al.*, 1976; Weidinger *et al.*, 1974). The results, when combined, indicate that 138 of 418 subjects treated with an average administered activity of 13.8 mCi of ^{125}I were hypothyroid at a mean followup time of 47 months. If, based on calculations of Maxon *et al.* (1977), one assumes (a) that the absolute risk of clinical hypothyroidism following therapy with ^{131}I for hyperthyroidism is 4.4 cases per million persons per rad per year; and (b) that all hyperthyroid subjects had a thyroid weight of 45 g

with a 65% thyroidal radioiodine uptake at 24 h and an effective half-life for ^{131}I of 6 days, then a similar mean administered activity of 13.8 mCi of ^{131}I would have been predicted to result in 136 cases of hypothyroidism in 418 subjects. These limited considerations suggest that ^{125}I is similar to ^{131}I in terms of the induction of hypothyroidism in humans at high radiation dose levels.

Consideration of these varied effects of ^{125}I on the thyroid gland does not permit the development of a risk estimate for carcinogenesis following exposure to ^{125}I. For radiation protection purposes, in this report ^{125}I will be assumed to result in the same risk, rad for rad, as ^{131}I.

7. Iodine-129

Iodine-129 in the environment is primarily derived from nuclear fuel activities, especially the processing of spent fuel elements and the handling and disposal of radioactive wastes. An evaluation of the release of ^{129}I from nuclear power production has been made by the NCRP (1983). Any ^{129}I released to the environment can serve as a potential source of thyroid gland irradiation via its transport through various foods to human populations (Soldat, 1976; Book *et al.*, 1977).

The low specific activity (0.17 μCi/mg) of ^{129}I and the restricted capacity of the normal human thyroid to store iodine (12 mg) (ICRP, 1975) limit the hazard from ^{129}I (Book, 1977). Similar conditions apply to animals; Book (1983) was unable to find any increase in thyroid tumors or decrease in longevity in a life-time study of rats continually fed ^{129}I in amounts calculated to deliver approximately 1 rad per day to the thyroid. The dose to the rat thyroid at median lifetime was 660 rads. The absence of effects was attributed to the low dose rate of ^{129}I. These results and the limitations attendant upon ^{129}I exposure noted above suggest that ^{129}I does not pose a meaningful threat of thyroid carcinogenesis in people.

8. Tellurium

Although the various radioisotopes of tellurium do not appear to concentrate significantly in the thyroid gland (Hollins, 1969), they may decay to form various isotopes of iodine (*e.g.*, $^{135}Te \rightarrow {}^{135}I$; $^{133}Te \rightarrow {}^{133}I$; $^{132}Te \rightarrow {}^{132}I$) which may, in turn, affect the thyroid gland. Thus only the radioiodine daughters of radiotellurium will be considered in this report.

9. Technetium-99m and Iodine-123

Technetium-99m as the pertechnetate ion and ^{123}I are used for medical imaging of the thyroid gland because they give superior image quality and lower radiation doses to the thyroid than ^{131}I (Task Force, 1978). Iodine-123 is distributed within the thyroid gland as other radioiodines. Although ^{99m}Tc-pertechnetate is selectively concentrated by the thyroid follicular cell, it is not incorporated into thyroid hormones stored in the colloid (Atkins *et al.*, 1968). Given these biological factors and the range of particulate radiations for these two radionuclides (see Section 10.1, Table 10.1F), ^{123}I might be expected to deliver most of its dose to the colloid whereas ^{99m}Tc-pertechnetate would deliver its dose within the thyroid follicular cell. On the basis of the probable microscopic dose distribution, ^{123}I would appear to be similar to ^{125}I whereas ^{99m}Tc-pertechnetate would be similar to the short-lived radioiodines.

Consideration of the average dose rate for delivery of a standard total dose to the thyroid (see Section 10.1, Table 10.1E) would suggest that both ^{123}I and ^{99m}Tc-pertechnetate are similar to the short-lived radioiodines. However, the activity required to deliver a specific total dose would be relatively large for ^{123}I and ^{99m}Tc-pertechnetate (see Section 10.1, Table 10.1C). In addition, ^{99m}Tc-pertechnetate is collected by the thyroid gland to a much lesser degree (about one-tenth) than radioiodine (Task Force, 1978).

Biological data on the carcinogenic potential of ^{123}I and ^{99m}Tc-pertechnetate are needed but are not available. In the absence of such data, ^{123}I and ^{99m}Tc-pertechnetate will be considered in this report to have an upper bound risk coefficient for thyroid carcinogenesis which is the same value as that for external x or γ radiation.

10. Aspects Involving the Classification of Internal Emitters Based on Physical and Biological Characteristics

10.1 Physical Characteristics

The physical and biological characteristics of the radionuclides under discussion represent important factors in determining the thyroidal dose per unit activity in the thyroid gland, dose rate, and microscopic dose distribution within the thyroid gland.

The mean dose to a target organ from an internal emitter uniformly deposited within a source organ is given by the expression (Snyder *et al.*, 1976):

$$\bar{D} = \tilde{A} \cdot S \tag{10-1}$$

where: $\bar{D}$ = mean absorbed dose in rads,

$$\begin{aligned} \tilde{A} &= \int A(t)dt = \text{cumulated activity in } \mu\text{Ci}\cdot\text{h} \\ &\quad \text{with } A(t) \text{ being the activity as a function of} \\ &\quad \text{time within the source organ, and} \\ S &= \text{the mean absorbed dose to the target organ} \\ &\quad \text{per unit cumulated activity in the source organ,} \\ &\quad (\text{rad}/\mu\text{Ci}\cdot\text{h}). \end{aligned} \tag{10-2}$$

S values for various radionuclides have been published (Snyder *et al.*, 1976) including values for the thyroid as both the source and the target (which are appropriate for calculation of the self dose to the thyroid).

The instantaneous mean dose rate, $d\bar{D}/dt$, is proportional to the activity present in the source organ with the constant of proportionality being S, namely:

$$d\bar{D}/dt = S \cdot A(t) \tag{10-3}$$

Thyroid-to-thyroid S values for the radionuclides of interest are given in Table 10.1A.

An average dose rate ($\bar{D}_R$) may be calculated from the expression:

$$\bar{D}_R = D_f/T = D_f \frac{\ln 2}{T_E \ln[D_t/(D_t - D_f)]} \quad (10\text{-}4)$$

where $\bar{D}_R$ is the average dose rate in rads per hour over the interval of time (T) required to deliver a specified fixed dose in rads (D_f) for each isotope, starting from an initial activity (A_0) uniformly distributed in the thyroid gland. D_t is the total dose delivered from an initial activity A_0 in the thyroid using a simple exponential model with an effective half-time T_E. Results for various radioisotopes are presented in Tables 10.1B, C, and D for different initial activity values in the thyroid. It should be noted that $\bar{D}_R$ is not directly proportional to A_0; however, under those conditions for which D_f is very much less than D_t, the value $\bar{D}_R$ will be approximately proportional to A_0. As D_f is increased, the shorter-lived radionuclides will experience a greater change in the relative value of $\bar{D}_R$.

An alternative method for comparing average dose rate would involve the specification of a standard total dose (instead of a standard initial activity). Under these conditions, the initial activity in the thyroid responsible for producing this total dose would depend upon the individual radioisotope. Table 10.1E provides the results for a value of the total dose equal to 100 rads. Under conditions for which

TABLE 10.1A—*Thyroid to thyroid S values, physical half lives, and effective half times*

Radionuclide	S Values (rad/μCi·h)[a] (Thyroid to Thyroid)	Physical Half Life (h)	$T_E(h)$[b] Effective Half Time in the Thyroid
^{99m}Tc	2.3×10^{-3}	6.02	2.4
^{123}I	4×10^{-3}	13.2	13.1
^{125}I	3×10^{-3}	1445	866
^{129}I	7.1×10^{-3}	1.49×10^{11}	2160
^{131}I	2.2×10^{-2}	193	177
^{132}I	6×10^{-2}	2.3	2.3
^{133}I	4.6×10^{-2}	20.3	20.1
^{135}I	4.5×10^{-2}	6.7	6.7

[a] From (Snyder, 1976) with the exception of that for ^{135}I which was determined directly from the ^{135}I: Nuclear Data Sheets (1975).

[b] Assuming a biological half time of 90 days for iodine and of 4 hours for ^{99m}Tc pertechnetate. For iodine, the biological half-times reported in the literature vary widely between mean values in adults of about 68 days (Wellman *et al.*, 1970) up to 108 days (Van Dilla and Fulwyler, 1964). For ^{99m}Tc, no comprehensive reference was found. One MIRD Report (1976) discusses multiple components with the initial clearance having a half-time of 1 to 2 hours; extrapolation of data from Fragu *et al.* (1982) would indicate a biological half-time for ^{99m}Tc-pertechnetate of about 2 to 6 hours.

TABLE 10.1B—*Average dose rate to the thyroid from an initial activity of 0.1 mCi in the gland*[a]

Radionuclide	D_t(rads) Total Dose Delivered to the Thyroid from 0.1 mCi Initially in the Gland	$T(h)$ Time in Which the Fixed Dose D_t from 0.1 mCi of Activity is Delivered				$\bar{D}_R$(rads/h) Average Dose Rate for Delivery of the Fixed Dose D_t from 0.1 mCi of Activity			
		D_t:	1 rad	10 rads	100 rads	D_t:	1 rad	10 rads	100 rads
^{99m}Tc	0.80		—	—	—		—	—	—
^{123}I	7.6		2.67	—	—		0.37	—	—
^{125}I	375		3.33	33.8	388		0.30	0.30	0.26
^{129}I	2213		1.41	14.1	144		0.71	0.71	0.69
^{131}I	563		0.45	4.6	50.0		2.20	2.18	2.00
^{132}I	19.9		0.17	2.3	—		5.84	4.31	—
^{133}I	133		0.22	2.3	40.1		4.59	4.43	2.49
^{135}I	43.4		0.22	2.5	—		4.45	3.96	—

[a] The effective half-times used are those in Table 10.1A

TABLE 10.1C—*Average dose rate to the thyroid from an initial activity of 1.0 mCi in the gland*[a]

Radionuclide	D_t(rads) Total Dose Delivered to the Thyroid from 1.0 mCi Initially in the Gland	$T(h)$ Time in Which the Fixed Dose D_f from 1.0 mCi of Activity is Delivered			$\bar{D}_R$(rads/h) Average Dose Rate for Delivery of the Fixed Dose D_f from 1.0 mCi of Activity			
		D_f:	1 rad	10 rads	100 rads	D_f:	1 rad	10 rads	100 rads
^{99m}Tc	8.0		0.46	—	—		2.2	—	—
^{123}I	75.7		0.25	2.7	—		4.0	3.7	—
^{125}I	3747		0.33	3.3	33.8		3.0	3.0	3.0
^{129}I	22125		0.14	1.4	14.1		7.1	7.1	7.1
^{131}I	5627		0.045	0.45	4.6		22.0	22.0	22.8
^{132}I	199		0.017	0.17	2.3		59.8	58.5	43.2
^{133}I	1335		0.022	0.22	2.3		46.0	45.9	44.3
^{135}I	434		0.022	0.22	2.5		45.0	44.5	39.6

[a] The effective half-times used are those in Table 10.1A

TABLE 10.1D—*Average dose rate to the thyroid from an initial activity of 10 mCi in the gland*[a]

Radionuclide	D_t(rads) Total Dose Delivered to the Thyroid from 10 mCi Initially in the Gland	$T(h)$ Time in Which the Fixed Dose D_t from 10 mCi of Activity is Delivered				D_R(rads/h) Average Dose Rate for Delivery of the Fixed Dose D_t from 10 mCi of Activity			
		D_t:	1 rad	10 rads	100 rads	D_t:	1 rad	10 rads	100 rads
^{99m}Tc	79.7		0.044	0.46	—		22.9	21.6	—
^{123}I	757		0.025	0.25	2.68		40.0	39.8	37.4
^{125}I	37468		0.033	0.33	3.34		30.0	30.0	30.0
^{129}I	221252		0.014	0.14	1.41		71.0	71.0	71.0
^{131}I	56274		0.0045	0.045	0.45		220.0	220.0	219.8
^{132}I	1991		0.0017	0.017	0.17		599.9	598.5	584.8
^{133}I	13346		0.0022	0.022	0.22		460.2	460.1	458.5
^{135}I	4336		0.0022	0.022	0.22		449.9	449.4	444.7

[a] The effective half-times used are those in Table 10.1A.

TABLE 10.1E—*Average dose rate to the thyroid while delivering a standardized total dose of 100 rads*

Radionuclide	$A_o(\mu Ci)$ Initial Activity in the Thyroid to Deliver a Total Thyroidal Dose of 100 rads	$T(h)$ Time in Which the Fixed Dose D_f is Delivered		$\bar{D}_R$(rads/h) Average Dose Rate for Delivery of the Fixed Dose (D_f)	
		D_f: 1 rad	10 rads	D_f: 1 rad	10 rads
^{99m}Tc	12541	0.035	0.37	28.7	27.4
^{123}I	1321	0.19	1.99	5.3	5.0
^{125}I	26.7	12.6	131.6	0.080	0.076
^{129}I	4.5	31.3	328.3	0.032	0.030
^{131}I	17.8	2.6	27.0	0.39	0.37
^{132}I	502	0.033	0.35	30.0	28.6
^{133}I	75	0.29	3.06	3.4	3.3
^{135}I	230	0.097	1.02	10.3	9.8

D_f is very much less than D_t, the value of $\bar{D}_R$ will be approximately proportional to D_t.

The distribution of dose within an organ will involve the mean number of particulate radiations per nuclear transition and the range of those particles in tissue. Table 10.1F provides a comparison of the fraction of dose delivered by particulate radiation relative to photon radiation and range characteristics for the particles in the thyroid tissue. Given the relatively constant proportion of dose delivered by particulate radiation from the radioisotopes under consideration, there remains the possibility that variations in carcinogenic response might be due to dose rate or to the dose distribution within the thyroid gland as reflected by the range characteristics.

The comparative data shown for the instantaneous dose rate per unit activity present (reflected by the S values in Table 10.1A), the average dose rate $\bar{D}_R$ per unit initial activity (Tables 10.1B, C, D), and the particle range considerations (Table 10.1F) suggest that the radionuclides might fall into two major categories—one including ^{132}I, ^{133}I, and ^{135}I and the other ^{99m}Tc, ^{123}I, ^{125}I, and ^{129}I with ^{131}I falling between the two groups. An extension of this approach would imply that the first group of radionuclides might have a more significant effect on the induction of thyroid cancer than the second. However, when standardized to a given total dose (Table 10.1E), the groupings change somewhat with ^{123}I and ^{99m}Tc appearing more similar to ^{132}I, ^{133}I, and ^{135}I since the average dose rate $\bar{D}_R$ for ^{99m}Tc and ^{123}I appears relatively

TABLE 10.1F—*Fraction of the thyroid dose delivered by particulate radiation. Particle range considerations*

Radionuclide	Fraction of Dose Delivered by Particulate Radiation[a]	R_{wt}(cm) Mean Range of Particles in the Thyroid[b]	R_{90}(cm) the Distance Within Which 90% of the Energy from Beta Emitters is Absorbed[c]
^{99m}Tc	0.79	0.016	—
^{123}I	0.77	0.012	—
^{125}I	0.73	0.0012	—
^{129}I	0.95	0.0034	0.0066
^{131}I	0.94	0.036	0.074
^{132}I	0.90	0.17	0.30
^{133}I	0.96	0.13	0.21
^{135}I	0.90	0.11	0.21

[a] Calculated using data from MIRD Dose Estimate Reports (MIRD 1975a, 1975b, 1984), Nuclear Data Sheets (1975), and Snyder *et al.* (1974)

[b] Weighted mean based on the mean number of all particles with an average energy greater than 0.01 MeV;

$R_{wt} = (\Sigma n_i r_{0i})/\sum n_i$

n_i = mean number of particles of energy type i per nuclear transition,

r_{0i} = the range within tissue of density 1g/cm^3 for a particle of energy type i, and

r_{0i}(cm) = 0.412 E_i (1.265 − 0.0954lnE_i) for energy; 0.01 ≤ E_i ≤ 2.5 MeV (Radiological Health Handbook, 1970);

For ^{129}I through ^{135}I, which are β^- emitters, the average β^- energy was used in the range calculation.

[c] The R_{90} values were calculated using the data from Table 3 on Beta-Ray Dose Rates in water from Cross *et al.* (1982). The tabulated doses in this reference include the β-spectra but go beyond Berger in MIRD Pamphlet No. 7 (1971) by including conversion electrons with intensities greater than 0.01.

high as a result of the increased initial activity required to produce the specified total dose.

10.2 Biological Effects

Dose Distribution

Central to the question of dose distribution considerations are differences in thyroidal and thyroid follicle sizes between and within species and distribution of iodine within the follicle. Within the normal

adult human thyroid gland, follicular size may range from 20 to 900 microns (average 200) (Gillespie *et al.*, 1970; Maximow and Bloom, 1957). The overall mass of thyroidal tissue in humans varies greatly with age until adulthood (Wellman *et al.*, 1970).

Fitzgerald and Foote (1949) found a marked variability in ^{131}I concentration in human thyroid follicles using autoradiographic analyses of tissue slices from patients undergoing surgery for thyroid disease. Sinclair *et al.* (1956) examined ^{131}I autoradiographs from the thyroids of patients operated on for a variety of thyroid diseases. In people with diffuse goiters (as opposed to nodular goiters which would be expected to be even more dissimilar from the normal thyroid), they found a large variation in dose distribution with a mean ratio between maximum and median dose of 3.3 to 1 (range: 2.4:1 to 7.7:1). Clayton (1953) estimated from autoradiographs of a normal rat thyroid that an interfollicular dose variation of as much as 5:1 can occur after ^{131}I administration. Klassovskii (1967) compared autoradiographs of rat thyroid glands following ^{131}I administration to those obtained after administering a mixture of radioiodines (80 percent ^{132}I and ^{133}I) and concluded that ^{131}I is 3 to 5 times less homogenous in distribution of radiation than the mixture of radioiodines.

On the other hand, Nadler and Leblond (1954) suggested that the turnover of iodine may be greater in smaller follicles than in larger ones, thus resulting in only apparent inhomogeneities in radiation dose as determined by autoradiographic studies at a fixed point in time. Anspaugh (1965) reviewed the problem and concluded that, in the normal human thyroid, dose distribution within the thyroid gland was uniform for ^{131}I whereas it would be expected to be non-uniform in diseased thyroid glands. Van Best (1981) has reported calculations of average thyroidal epithelial cell doses from various radioiodines, including ^{123}I, ^{125}I, and ^{131}I, in thyroid follicles. The ratios between average follicular cell dose and average thyroidal gland dose were close to unity for ^{131}I whereas large differences were calculated for ^{125}I. Thus, inhomogeneities in the distribution of ^{131}I in the human thyroid gland would appear to be important only when macroscopic variations in follicle size occur, and microscopic variations would appear to have little effect. For other radioiodines such as ^{125}I or ^{129}I, dose distribution within the thyroid gland may be more important.

Dose Rate

The effect of dose rate on malignant transformation in a thyroid cell has been considered to be of greater importance than dose distri-

bution by both Anspaugh (1965) and Walinder *et al.* (1971). Malone (1975) has reviewed the problem and has concluded that the dose rate is a major factor in the inefficiency of ^{131}I in causing biological changes in the thyroid. He indicated that, in the rat, peak dose rates for ^{131}I are in the range of 10 to 400 rads/hour and decline rapidly as ^{131}I is eliminated from the gland. At dose rates less than about 100 rads/hour, the shoulder of the cell-survival curve vanishes because repair of sublethal damage has time to take place during irradiation and more absorbed dose is required to produce an equivalent effect. However, he also found that the ratio of dose of ^{131}I to x rays required to achieve a particular effect is larger than that usually associated with dose rate alone.

The two factors of dose rate and dose distribution may both be important, depending on the type of exposure and the function and anatomy of the thyroid gland being irradiated. Similar conclusions were reached by Saenger *et al.* (1963) in their analysis of human thyroidal carcinogenesis following exposure to ^{131}I or to x rays.

In their re-evaluation of thyroidal carcinogenesis in children irradiated for alleged thymic enlargement, Shore *et al.* (1980) examined the effects of dose fractionation on thyroid cancer induction. The yield of thyroid cancers per rad at doses per fraction which were greater than 200 rads was about four times greater than that at doses per fraction below 200 rads. A similar probable dose-rate effect was observed by Maxon *et al.* (1980) who noted an increase in cancer yield in irradiated children that was disproportionately larger than differences in total thyroidal dose as the number of x-ray treatments increased. In both studies, dose distribution in the children's thyroid glands would be expected to be uniform from the x-ray therapy techniques employed.

10.3 Effectiveness of x-irradiation, ^{131}I, and Short-Lived Radioiodines: Non-Carcinogenic Effects

Thyroidal effects other than carcinogenesis also indicate that there are differences in the effectiveness of the radiation from ^{131}I and external x irradiation (Table 5.1). Based on a comparison of histopathologic changes in irradiated thyroids of sheep, McClellan *et al.* (1963) estimated ^{131}I to be about one-twentieth as effective as x rays. In mice, using the inhibition of goitrogenic stimulation as the index of radiation effect, ^{131}I was found to be one-fourth to one-half as

effective as x rays (Walinder and Sjoden, 1971). Similarly obtained data on rats of Greig *et al.* (1970), mentioned above, suggest that ^{131}I is about one-eighth as effective as x radiation.

Differences in the effectiveness of thyroid gland irradiation also have been observed in studies in which the short-lived radioiodines, ^{132}I, ^{133}I, and ^{135}I were compared to ^{131}I. These short-lived isotopes of iodine may be assumed to deliver radiation to the thyroid in a manner similar to that of x irradiation since their energetic emissions would result in a fairly uniform distribution of dose and their short half-lives would result in comparatively high dose rates (Table 5.1).

Klassovskii *et al.* (1970) compared the effects of irradiation of the thyroid gland in rats and dogs with ^{131}I and with mixtures comprised of 20 percent ^{131}I and 80 percent a combination of ^{132}I, ^{133}I, and ^{135}I, similar to those thought to have been present in radioactive fallout from nuclear weapons tests near the Marshall Islands. They concluded that the effects of irradiation of the gland with ^{131}I were only one-tenth to one-twentyfifth times as pronounced as those seen following irradiation with the mixture of radioiodines based upon histologic effects, alterations in iodine uptake, changes in thyroid size, and tumor formation.

Book *et al.* (1980a) found that ^{131}I was one-ninth as effective as ^{132}I in inhibiting the thyroidal response of rats to goitrogenic stimulation. These results were similar to those of Walinder and Sjoden (1971 and 1972) in which ^{131}I was found to be one-half to one-tenth as effective as x-ray in goitrogenic inhibition in the mouse. Walinder *et al.* (1972) also found that ^{132}I and x-ray appeared to be of similar effectiveness in the inhibition of goitrogenesis in the mouse.

The only published studies of a human population exposed to large amounts of short-lived highly energetic radioiodines are those reviewing the experience of the Marshall Islanders exposed to fallout. James (1972) and Conard (1982) have suggested that the effects of the shorter-lived isotopes appeared to be more like those predicted from external radiation exposure than from exposure to ^{131}I alone. Evaluation of this group is not easy because of a lack of data defining the isotopes responsible for the internal irradiation of the thyroid gland and because they also received external whole body irradiation. In addition, thyroid hormone was prescribed for some people but not necessarily taken as prescribed.

There is an obvious need for further specific radiobiologic research into the relative carcinogenicity of various iodine isotopes before more firm risk estimates can be made.

11. Conclusion and Recommendations: Carcinogenic Risk to the Human Thyroid Following Exposure to Ionizing Irradiation in Doses of Less than 1500 Rads

The best human information regarding thyroidal radiation carcinogenesis is based on studies of children exposed to external radiation. It is recommended that those data be used, with modification for application to internal emitters, as the basis for risk calculations. Data suggesting that children are more susceptible than adults warrant a 50 percent reduction in risk coefficients when estimates derived for people less than or equal to 18 years of age at exposure are applied to a population of adults. Women appear to have at least twice the risk of men for clinically apparent cancers at a given exposure level.

Human experience and much animal data suggest that ^{131}I is less carcinogenic to the thyroid, per rad of absorbed dose, than external radiation. This difference in effectiveness is probably due to factors related to dose rate and to dose distribution. It is recommended that ^{131}I be considered to be no more than one-third as effective as external radiation in the induction of thyroid cancer in the general population. The value of one-third may overestimate the actual risk of ^{131}I but is considered to be suitable for calculation of the upper limit of the risk estimate for radiation protection purposes.

The general formula used to calculate age, sex, and radiation source specific risks is shown in Table 11.1. A test of that model

TABLE 11.1—*Model for calculation of age, sex, and radiation source specific risk estimates for thyroidal carcinogenesis*

$$\text{Specific Risk Estimate} = R \cdot F \cdot S \cdot A \cdot Y \cdot L \qquad (11\text{-}1)$$

Where:

the Specific risk estimate is for thyroid cancer attributable to radiation exposure,

R = Absolute risk estimate (excess cases per 10^6 persons per rad per year) for consigned (both sexes), ethnically similar, populations of children exposed to external x irradiation and correcting for a minimum induction period for thyroid cancer of 5 years,

F = Dose effectiveness reduction factor (1 for external radiation, ^{132}I, ^{133}I, and ^{135}I; 1/3 for ^{131}I and ^{125}I),

S = Sex factor (4/3 for women and 2/3 for men, assuming that women are twice as susceptible as men and that the R was derived from a population comprised of equal numbers of both sexes),

A = Age factor (1 for populations age 18 or less at exposure and 1/2 for populations over age 18 at exposure),

Y = Anticipated average number of years at risk for the population in question, and

L = Lethality (assume a maximum lifetime lethality of 1/10). Use this factor only when calculating the specific risk estimate for life-time deaths due to thyroid cancer.

using Marshallese data (Appendix C) shows good agreement between predicted and observed excess thyroid cancers, despite the stated limitations of the Marshallese data.

While risk estimates derived from pooled data are useful when considering the effects of exposure, factors related to heritage appear to be important. Hence, risk factors from controlled studies of populations similar to the one at risk should be used whenever possible.

For the calculation of risks of fatal cancer, current levels of medical diagnosis and care are assumed, and a maximum of 10 percent of the clinically evident radiation-induced thyroid cancers are expected to be lethal.

Tables 11.2 and 11.3 give risk estimates that are considered to be applicable to the population of the U.S. for mean thyroidal doses in the range from 6 to 1500 rads. The absolute risk estimate used (2.5 cases per million persons per rad per year at risk) is based on population studies of North Americans exposed to external radiotherapy in childhood. The specific risk estimate adjustments shown in Table 11.1 and the age-sex specific years at risk shown in Table 2.1 have been applied. Following exposure

TABLE 11.2—*Annual risk in total and lethal excess thyroid cancers per million persons per rad of thyroid dose for doses from 6 to 1500 rads (United States population)*[a]

Source of Irradiation	Persons over age 18 years at time of exposure				Persons age 18 or less years at time of exposure			
	TOTAL		LETHAL		TOTAL		LETHAL	
	Male	Female	Male	Female	Male	Female	Male	Female
^{131}I, ^{125}I	0.28	0.56	0.028	0.056	0.56	1.12	0.056	0.112
External x or gamma rays and ^{132}I, ^{133}I, and ^{135}I	0.84	1.68	0.084	0.168	1.68	3.36	0.168	0.336

[a] Based on an absolute risk estimate of 2.5 cases per 10^6 persons per rad per year in people exposed to external irradiation in childhood and modified according to the model shown in Table 11.1.

TABLE 11.3—*Total and lethal excess thyroid cancers over the lifetimes of a general population of one million persons per rad of thyroid dose for doses from 6 to 1500 rads (United States population)*[a]

Source of Irradiation	Persons over age 18 years at time of exposure				Persons age 18 or less years at time of exposure			
	TOTAL		LETHAL		TOTAL		LETHAL	
	Male	Female	Male	Female	Male	Female	Male	Female
^{131}I, ^{125}I	2.74	6.80	0.274	0.680	4.83	10.5	0.483	1.05
External x or gamma rays and ^{132}I, ^{133}I, and ^{135}I	8.22	20.4	0.822	2.04	14.5	31.5	1.45	3.15

[a] To obtain a lifetime risk estimate for the United States population, each annual risk estimate in Table 11.2 was multiplied by the total lifetime years at risk for that subgroup shown in Table 2.1, item 6.

to external irradiation the projected overall lifetime incidence of fatal thyroid cancer would be 7.5 cases per rad in a general population of one million persons. This estimate is consistent with earlier lifetime estimates from the UNSCEAR (1977) report (5 to 15 cases), the ICRP (1977) report (5 cases) and the BEIR (1980) report (6 to 18 cases) for similar exposures.

APPENDIX A

Comments on Absolute vs. Relative Risk Estimates

One problem of any risk estimate procedure is that of projecting risk beyond the period of observation. There are no human data to suggest that the incidence of radiation associated thyroid cancer will continue to increase in a linear manner indefinitely. Indeed there are very preliminary indicators that the incidence may decrease after about 40 years. For thyroid cancer, there is the additional difficulty that estimates of effects are based almost entirely on persons exposed to external x irradiation early in childhood. Finally there are apparent differences in the so-called "natural incidence" in groups of differing sex, age, and heritage. It was judged that a relative risk calculation for thyroid cancer might be particularly susceptible to these factors, with resultant overestimation of risk. At the same time, it was obvious that while an absolute risk calculation might be less affected by these factors, a single value of absolute risk for all circumstances was not realistic. The concept of a specific risk estimate based on an absolute risk coefficient modified by other specific, relevant factors, was considered best.

To help evaluate this hypothesis, a Staff Scientist in the Statistics Section of Battelle Pacific Northwest Laboratory was asked to evaluate the data.[1] She developed a life table analysis for the United States based on the 1978 age distribution in the United States (Vital Statistics, 1981) and used data from the SEER Registries (Young *et al.*, 1981) to estimate spontaneous cases (Table A.1). Using the data in Table A.1, she then calculated the number of excess, external radiation associated cancers which would be projected by a life table analysis with an absolute model using risk estimates of 2.5 and 1.25 cases per million persons per rad per year (depending on age). This resulted in a lifetime projection of 72.1 cases per million persons per rad. The estimates from Table 11.3 in this report using the specific risk calcu-

[1] The NCRP is appreciative of the efforts of Dr. Ethel S. Gilbert of Battelle Pacific Northwest Laboratory in this matter.

TABLE A.1—*Lifetime risks of spontaneous thyroid cancer*[a]

	Parameter	AGE GROUP	
		0–19	20 +
(1)	Proportion of population	0.328	0.672
(2)	Average life expectancy beyond a 5-year minimum induction period (years)	59.0	28.2
(3)	Person-years contributed by age group per million total population (1) × (2) × (population)	19.35×10^6	18.95×10^6
(4)	Spontaneous cases per 10^6 persons of thyroid cancer expected beyond a 5-year minimum induction period	3534.5	1985.9
(5)	Spontaneous cases contributed by age group in total population of 10^6 persons (1) × (4)	1159.3	1334.5

[a] Based on the 1978 age distribution of the U.S. population and 1978 life tables for the U.S.

lation would project 74.6 cases per million persons per rad for a population comprised equally of men and women. She also prepared a lifetime estimate based on a relative risk model in which it was assumed that the actual observed number of excess cases over the approximate period of observation of 5 to 30 years post exposure was the same for both the relative and the absolute risk model for each of the two age groups. The resultant lifetime estimate of excess cancers was 86.6 cases per million persons per rad.

It is evident that the absolute, relative and specific risk estimate models yield similar results. The specific risk estimate model used in this report (Table 11.1) is considered to most clearly demonstrate the various factors on which practical risk calculations depend and, therefore, to result in a realistic model for use until better data become available.

APPENDIX B

Approximate Time of Death due to Thyroid Cancer in Irradiated Patients

The times at which deaths from papillary and follicular thyroid cancer occur may be important in predicting the course and outcome for populations of affected people. Two of the largest experiences are those from the Mayo Clinic (McConahey *et al.*, 1981) and the Lahey Clinic (Cady B, *et al.*, 1976). The Mayo Clinic series included 820 patients with papillary carcinoma and 174 patients with follicular carcinoma treated between 1946 and 1971. The Lahey Clinic series included 423 patients with papillary carcinoma and 178 patients with follicular carcinoma treated between 1931 and 1970. The distribution of deaths due to thyroid cancer for 1595 patients in the two populations is shown in Table B.1. The proportion of follicular carcinomas (22 percent) was about twice what would be predicted for radiation-associated thyroid cancers (10 percent).

If the average values for the percent of deaths during each time interval (Table B.1) are weighted according to the projected distributions of death due to each histologic type of thyroid cancer following

TABLE B.1—*Time distribution of deaths due to papillary or follicular carcinoma of the thyroid*

Time After Diagnosis (Years)	Papillary Carcinoma			Follicular Carcinoma		
	Mayo Clinic	Lahey Clinic	Arithmetic Mean	Mayo Clinic	Lahey Clinic	Arithmetic Mean
0–5	40%[a]	48%	44%	53%	49%	51%
6–10	30%	14%	22%	7%	27%	17%
11–15	—	21%	10.5%	7%	10%	8.5%
16–20	—	7%	3.5%	33%	8%	20.5%
21 or more	30%	10%	20%	—	6%	3%

[a] Percent of total lifetime deaths occurring in each time interval.

TABLE B.2—*Estimated time distribution of deaths due to radiation-associated thyroid carcinoma*

Time After Diagnosis (Years)	Papillary Carcinoma	+ Follicular Carcinoma	= Total
0–5	33%*	13%	46%
6–10	16%	4%	20%
11–15	8%	2%	10%
16–20	3%	5%	8%
21 or more	15%	1%	16%
Total	75%	25%	100%

* Percent of total lifetime deaths occurring in each time interval.

irradiation (3/4 due to papillary and 1/4 due to follicular cancer) (Table 3.5), then an estimate of the time of death due to radiation-associated thyroid cancer may be obtained (Table B.2). These approximations are not appropriate for application to individual cases of thyroid cancer. For individuals, factors such as age at diagnosis, sex, size of the primary cancer, extent of invasion or spread at diagnosis, degree of cellular differentiation of the primary cancer, and type of treatment would be important in determining outcome (McConahey *et al.*, 1981; Cady *et al.*, 1976; Byar *et al.*, 1979).

APPENDIX C

A Test of the Model Based on Experience in Marshall Islanders Exposed to Mixed Types of Irradiation (Predominately External Gamma Radiation, Short Lived Radioiodines, and Radiotellurium)

Because of the limitations of the Marshallese data, as pointed out in Section 10.3, that data is not used to derive risk estimates. However, it is considered useful to use that data in a test of the model for specific risk estimates shown in Table 11.1.

Based on preliminary communications regarding the most recent follow-up of the Marshallese and their revised dosimetry (Lessard, 1983), the proposed model for thyroid cancer induction would predict a total of 5 excess thyroid cancers (Table C.1), using as the base an absolute risk estimate of 2.5 cases per million persons per rad per year at risk in children exposed to external radiation modified for age at exposure and years at risk as indicated in Table 11.1. In fact, 6 or 7 cases of thyroid cancer have been found in the irradiated group (depending on how one lesion is classified), whereas about 2 cases were expected without radiation (based on the unexposed population). This results in a radiation-associated excess of four or five cases

TABLE C.1—*Observed and predicted thyroid cancer in irradiated Marshall Islanders*[a]

Age at Exposure (Years)	Number	Approximate Mean Total Thyroid Dose (rads)[b]	Approximate Mean Years at Risk[c]	Predicted Number of Excess Cancers[d]	Observed Number of Excess Cancers[d]
≤ 18	122	1130	12.7	4	2
> 18	129	470	15.0	1	2
Entire Population	251	790	13.9	5	4

[a] Using an absolute risk of 2.5 cases per 10^6 persons per rad per year for children and 50% of that value for exposure later in life.

[b] Based on current revisions at Brookhaven (Lessard *et al.*, 1983). The total dose is predominantly from short lived radioiodines and external gamma, with external radiation comprising no more than 30% of the total dose and in most cases much less.

[c] Assumed to be time from exposure to time of surgery or follow-up minus a 5 year minimum induction period.

[d] Rounded to whole numbers. The malignant or benign nature of one of the excess observed tumors in the ≤ age 18 group is debated, but it has been classified as cancer in the past (Conard, *et al.* 1980). However it is currently regarded as benign after another review of pathology (Lessard *et al.*, 1983). If it were classified as malignant, the observed excess cancers would be 5.

assuming that the majority of the total dose was due to sources other than ^{131}I (Lessard *et al.*, 1983). These findings confirm the postulate that short-lived, relatively high energy isotopes of iodine have a carcinogenic effect in man similar to that of external gamma radiation. Although the occurrence of thyroid cancer may have been altered by thyroid hormonal and/or surgical therapy, De Groot *et al.* (1983) have recently indicated that thyroid hormone administration beginning a number of years after external radiation exposure does not appear to protect the individual against the subsequent appearance of radiation-associated thyroid cancer.

APPENDIX D

Glossary

absolute risk: Expression of excess risk due to exposure as the arithmetic difference between the risk among those exposed and that obtaining in the absence of exposure. The resultant risk coefficient is normalized to a population base of 1 million people and is expressed as number of excess cases per million persons per rad per year at risk. Absolute risk coefficients project a constant level of excess risk over the period of expression.

alpha errors: Type I errors of statistical hypothesis testing. The probability that a null or test hypothesis will be incorrectly rejected in an instance of hypothesis testing. The probability that a difference will be found to exist when, in fact, there is no true difference.

biological half-time: The amount of time required for a biological system (in this report usually human beings) or organ to eliminate one-half of the material in question.

effective half-time: The time in which the radionuclide within an organ decreases by one half as a result of radioactive decay and biological elimination.

excess cases: The difference between the number of cases of thyroid cancer occurring in an irradiated population and the number of thyroid cancer cases occurring in a similar non-irradiated population over the same time period.

goiter: Enlargement of part or all of the thyroid gland.

Graves' disease: A disease state in which the thyroid gland enlarges and may produce excessive amounts of thyroid hormone. Currently considered to represent an autoimmune disease which is caused by the formation of abnormal immunoglobulin stimulators of the thyroid gland.

heritage: A term collectively referring to the influence of species, genetic background, ethnic group, and environment on susceptibility to thyroid carcinoma.

hyperthyroidism (thyrotoxicosis): Functional, metabolic state caused by excessive thyroid hormone.

hypothyroidism: Functional, metabolic state caused by inadequate amounts of thyroid hormone.

incidence: The rate at which new cases of a disease develop during some specified time period. The number of new cases of disease found in a population measured over a period of time.

minimum induction period: The period of time between radiation exposure and the detection of the first excess case of thyroid cancer following radiation exposure (sometimes called latent period).

physical half-life: The time in which half the nuclei of a particular radionuclide decay; hence, the time in which the activity decreases to half its initial value.

prevalence: The rate of existing cases of disease in a population at a particular point in time.

rad: The unit of absorbed dose involving the energy absorbed from ionizing radiation per unit mass of any material. One rad equals 100 ergs per gram.

relative risk: Expression of risk due to exposure as the ratio of the risk among the exposed to that obtaining in the absence of exposure. Relative risk coefficients distribute the radiogenic excess in the pattern of the natural incidence or mortality over the interval of expression.

Roentgen (R): The unit of radiation exposure representing the charge liberated by the radiation per unit mass of air. One Roentgen equals 2.58×10^{-4} coulomb per kilogram of air.

specific risk: A risk model that involves numerous modifications of an absolute risk model to account for age at exposure, sex, and source of radiation.

years at risk: The difference between the time that has elapsed between radiation exposure and the endpoint of the period of observation and the minimum induction period. The maximum number of years at risk includes the period of observation plus the anticipated average remaining lifespan of the population in question minus the minimum induction period.

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The NCRP

The National Council on Radiation Protection and Measurements is a nonprofit corporation chartered by Congress in 1964 to:

1. Collect, analyze, develop, and disseminate in the public interest information and recommendations about (a) protection against radiation and (b) radiation measurements, quantities, and units, particularly those concerned with radiation protection;
2. Provide a means by which organizations concerned with the scientific and related aspects of radiation protection and of radiation quantities, units, and measurements may cooperate for effective utilization of their combined resources, and to stimulate the work of such organizations;
3. Develop basic concepts about radiation quantities, units, and measurements, about the application of those concepts, and about radiation protection;
4. Cooperate with the International Commission on Radiological Protection, the International Commission on Radiation Units and Measurements, and other national and international organizations, governmental and private, concerned with radiation quantities, units, and measurements and with radiation protection.

The Council is the successor to the unincorporated association of scientists known as the National Committee on Radiation Protection and Measurements and was formed to carry on the work begun by the Committee.

The Council is made up of the members and the participants who serve on the eighty-one Scientific Committees of the Council. The Scientific Committees, composed of experts having detailed knowledge and competence in the particular area of the Committee's interest, draft proposed recommendations. These are then submitted to the full membership of the Council for careful review and approval before being published.

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Currently, the following subgroups are actively engaged in formulating recommendations:

SC-1:	Basic Radiation Protection Criteria
SC-3:	Medical X-Ray, Electron Beam and Gamma-Ray Protection for Energies Up to 50 MeV (Equipment Performance and Use)
SC-16:	X-Ray Protection in Dental Offices
SC-18:	Standards and Measurements of Radioactivity for Radiological Use
SC-38:	Waste Disposal
	Task Group on Krypton-85
	Task Group on Carbon-14
	Task Group on Disposal of Accident Generated Waste Water
	Task Group on Disposal of Low-Level Waste
	Task Group on the Actinides
	Task Group on Xenon
	Task Group on Definitions of Radioactive Waste
SC-40:	Biological Aspects of Radiation Protection Criteria
	Task Group on Atomic Bomb Survivor Dosimetry
	Subgroup on Biological Aspects of Dosimetry of Atomic Bomb Survivors
SC-44:	Radiation Associated with Medical Examinations
SC-45:	Radiation Received by Radiation Employees
SC-46:	Operational Radiation Safety
	Task Group 1 on Warning and Personnel Security Systems
	Task Group 2 on Uranium Mining and Milling—Radiation Safety Program
	Task Group 3 on ALARA for Occupationally Exposed Individuals in Clinical Radiology
	Task Group 4 on Calibration of Survey Instrumentation
	Task Group 5 on Maintaining Personnel Exposure Records
	Task Group 6 on Radiation Protection for Allied Health Personnel
SC-47:	Instrumentation for the Determination of Dose Equivalent
SC-48:	Apportionment of Radiation Exposure
SC-52:	Conceptual Basis of Calculations of Dose Distributions
SC-53:	Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Radiation
SC-54:	Bioassay for Assessment of Control of Intake of Radionuclides
SC-55:	Experimental Verification of Internal Dosimetry Calculations
SC-57:	Internal Emitter Standards
	Task Group 2 on Respiratory Tract Model
	Task Group 3 on General Metabolic Models
	Task Group 6 on Bone Problems
	Task Group 8 on Leukemia Risk
	Task Group 9 on Lung Cancer Risk
	Task Group 10 on Liver Cancer Risk

Task Group 11 on Genetic Risk
Task Group 12 on Strontium
Task Group 13 on Neptunium
SC-59: Human Radiation Exposure Experience
SC-61: Radon Measurements
SC-63: Control of Exposure to Ionizing Radiation from Accident or Attack
SC-64: Radionuclides in the Environment
Task Group 5 on Public Exposure to Nuclear Power
Task Group 6 on Screening Models
Task Group 7 on Soil Contamination as a Source of Radiation Exposure
SC-65: Quality Assurance and Accuracy in Radiation Protection Measurements
SC-67: Biological Effects of Magnetic Fields
SC-68: Microprocessors in Dosimetry
SC-69: Efficacy Studies in Diagnostic Radiology
SC-70: Quality Assurance and Measurement in Diagnostic Radiology
SC-71: Radiation Exposure and Potentially Related Injury
SC-72: Radiation Protection in Mammography
SC-74: Radiation Received in the Decontamination of Nuclear Facilities
SC-75: Guidance on Radiation Received in Space Activities
SC-76: Effects of Radiation on the Embryo-Fetus
SC-77: Guidance on Occupational and Public Exposures Resulting from Diagnostic Nuclear Medicine Procedures
SC-78: Practical Guidance on the Evaluation of Human Exposures to Radiofrequency Radiation
SC-79: Extremely Low-Frequency Electric and Magnetic Fields
SC-80: Radiation Biology of the Skin (Beta-Ray Dosimetry)
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Task Group on Comparative Carcinogenicity of Pollutant Chemicals
Task Force on Occupational Exposure Levels
Ad Hoc Group on Model Used for Assessing Transport of Low Level Radioactive Waste
Ad Hoc Group on Medical Evaluation of Radiation Workers

In recognition of its responsibility to facilitate and stimulate cooperation among organizations concerned with the scientific and related aspects of radiation protection and measurement, the Council has created a category of NCRP Collaborating Organizations. Organizations or groups of organizations that are national or international in scope and are concerned with scientific problems involving radiation quantities, units, measurements and effects, or radiation protection may be admitted to collaborating status by the Council. The present Collaborating Organizations with which the NCRP maintains liaison are as follows:

American Academy of Dermatology
American Association of Physicists in Medicine
American College of Nuclear-Physicians
American College of Radiology
American Dental Association
American Industrial Hygiene Association
American Institute of Ultrasound in Medicine
American Insurance Association
American Medical Association
American Nuclear Society
American Occupational Medical Association
American Podiatric Medical Association
American Public Health Association
American Radium Society
American Roentgen Ray Society
American Society of Radiologic Technologists
American Society for Therapeutic Radiology and Oncology
Association of University Radiologists
Atomic Industrial Forum
Bioelectromagnetics Society
College of American Pathologists
Federal Communications Commission
Federal Emergency Management Agency
Genetics Society of America
Health Physics Society
National Bureau of Standards
National Electrical Manufacturers Association
Radiation Research Society
Radiological Society of North America
Society of Nuclear Medicine
United States Army
United States Air Force
United States Department of Energy
United States Department of Housing and Urban Development
United States Department of Labor
United States Environmental Protection Agency
United States Navy
United States Nuclear Regulatory Commission
United States Public Health Service

The NCRP has found its relationships with these organizations to be extremely valuable to continued progress in its program.

Another aspect of the cooperative efforts of the NCRP relates to the special liaison relationships established with various governmental organizations that have an interest in radiation protection and measurements. This liaison relationship provides: (1) an opportunity for participating organizations to designate an individual to provide liaison between the organization and the NCRP; (2) that the individual designated will receive copies of draft NCRP reports (at the time that

these are submitted to the members of the Council) with an invitation to comment, but not vote; and (3) that new NCRP efforts might be discussed with liaison individuals as appropriate, so that they might have an opportunity to make suggestions on new studies and related matters. The following organizations participate in the special liaison program:

Defense Nuclear Agency
Federal Emergency Management Agency
National Bureau of Standards
Office of Science and Technology Policy
Office of Technology Assessment
United States Air Force
United States Army
United States Coast Guard
United States Department of Energy
United States Department of Health and Human Services
United States Department of Labor
United States Department of Transportation
United States Environmental Protection Agency
United States Navy
United States Nuclear Regulatory Commission

The NCRP values highly the participation of these organizations in the liaison program.

The Council's activities are made possible by the voluntary contribution of time and effort by its members and participants and the generous support of the following organizations:

Alfred P. Sloan Foundation
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United States Environmental Protection Agency
United States Navy
United States Nuclear Regulatory Commission

To all of these organizations the Council expresses its profound appreciation for their support.

Initial funds for publication of NCRP reports were provided by a grant from the James Picker Foundation and for this the Council wishes to express its deep appreciation.

The NCRP seeks to promulgate information and recommendations based on leading scientific judgment on matters of radiation protection and measurement and to foster cooperation among organizations concerned with these matters. These efforts are intended to serve the public interest and the Council welcomes comments and suggestions on its reports or activities from those interested in its work.

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Lauriston S. Taylor Lectures

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2	*Why be Quantitative About Radiation Risk Estimates?* by Sir Edward Pochin (1978)
3	*Radiation Protection—Concepts and Trade Offs* by Hymer L. Friedell (1979) [Available also in *Perceptions of Risk,* see above]
4	*From "Quantity of Radiation" and "Dose" to "Exposure" and "Absorbed Dose"—An Historical Review* by Harold O. Wyckoff (1980) [Available also in *Quantitative Risks in Standards Setting,* see above]
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6	*Ethics, Trade-offs and Medical Radiation* by Eugene L. Saenger (1982) [Available also in *Radiation Protection and New Medical Diagnostic Approaches,* see above]
7	*The Human Environment-Past, Present and Future* by Merril Eisenbud (1983) [Available also in *Environmental Radioactivity,* see above]
8	*Limitation and Assessment in Radiation Protection* by Harald H. Rossi (1984) [Available also in *Some Issues Important in Developing Basic Radiation Protection Recommendations,* see above]
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The following NCRP Reports are now superseded and/or out of print:

No.	Title
1	*X-Ray Protection* (1931). [Superseded by NCRP Report No. 3]
2	*Radium Protection* (1934). [Superseded by NCRP Report No. 4]
3	*X-Ray Protection* (1936). [Superseded by NCRP Report No. 6]
4	*Radium Protection* (1938). [Superseded by NCRP Report No. 13]
5	*Safe Handling of Radioactive Luminous Compounds* (1941). [Out of Print]
6	*Medical X-Ray Protection Up to Two Million Volts* (1949). [Superseded by NCRP Report No. 18]
7	*Safe Handling of Radioactive Isotopes* (1949). [Superseded by NCRP Report No. 30]
9	*Recommendations for Waste Disposal of Phosphorus-32 and Iodine-131 for Medical Users* (1951)
10	*Radiological Monitoring Methods and Instruments* (1952). [Superseded by NCRP Report No. 57]
11	*Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water* (1953). [Superseded by NCRP Report No. 22]
12	*Recommendations for the Disposal of Carbon-14 Wastes* (1953). [Superseded by NCRP Report No. 81]
13	*Protection Against Radiations from Radium, Cobalt-60 and Cesium-137* (1954). [Superseded by NCRP Report No. 24]
14	*Protection Against Betatron—Synchrotron Radiations Up to 100 Million Electron Volts* (1954). [Superseded by NCRP Report No. 51]
15	*Safe Handling of Cadavers Containing Radioactive Isotopes* (1953). [Superseded by NCRP Report No. 21]

17 *Permissible Dose from External Sources of Ionizing Radiation* (1954) including *Maximum Permissible Exposure to Man, Addendum to National Bureau of Standards Handbook 59* (1958). [Superseded by NCRP Report No. 39]

18 *X-Ray Protection* (1955). [Superseded by NCRP Report No. 26]

19 *Regulation of Radiation Exposure by Legislative Means* (1955). [Out of Print]

20 *Protection Against Neutron Radiation Up to 30 Million Electron Volts* (1957). [Superseded by NCRP Report No. 38]

21 *Safe Handling of Bodies Containing Radioactive Isotopes* (1958). [Superseded by NCRP Report No. 37]

24 *Protection Against Radiations from Sealed Gamma Sources* (1960). [Superseded by NCRP Report Nos. 33, 34, and 40]

26 *Medical X-Ray Protection Up to Three Million Volts* (1961). [Superseded by NCRP Report Nos. 33, 34, 35, and 36]

28 *A Manual of Radioactivity Procedures* (1961). [Superseded by NCRP Report No. 58]

29 *Exposure to Radiation in an Emergency* (1962). [Superseded by NCRP Report No. 42]

31 *Shielding for High Energy Electron Accelerator Installations* (1964). [Superseded by NCRP Report No. 51]

34 *Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV—Structural Shielding Design and Evaluation* (1970). [Superseded by NCRP Report No. 49]

Other Documents

The following documents of the NCRP were published outside of the NCRP Reports series:

"Blood Counts, Statement of the National Committee on Radiation Protection," Radiology 63, 428 (1954)

"Statements on Maximum Permissible Dose from Television Receivers and Maximum Permissible Dose to the Skin of the Whole Body," Am. J. Roentgenol., Radium Ther. and Nucl. Med. 84, 152 (1960) and Radiology 75, 122 (1960)

X-Ray Protection Standards for Home Television Receivers, Interim Statement of the National Council on Radiation Protection and Measurements (National Council on Radiation Protection and Measurements, Washington, 1968)

Specification of Units of Natural Uranium and Natural Thorium (National Council on Radiation Protection and Measurements, Washington, 1973)

NCRP Statement on Dose Limit for Neutrons (National Council on Radiation Protection and Measurements, Washington, 1980)

Krypton-85 in the Atmosphere—With Specific Reference to the Public Health Significance of the Proposed Controlled Release at Three Mile Island (National Council on Radiation Protection and Measurements, Washington, 1980)

Preliminary Evaluation of Criteria For the Disposal of Transuranic Contaminated Waste (National Council on Radiation Protection and Measurements, Bethesda, Maryland, 1982)

Screening Techniques for Determining Compliance with Environmental Standards (National Council on Radiation Protection and Measurements, Bethesda, Maryland, 1986)

Control of Air Emissions of Radionuclides (National Council on Radiation Protection and Measurements, Bethesda, Maryland, 1984)

Copies of the statements published in journals may be consulted in libraries. A limited number of copies of the remaining documents listed above are available for distribution by NCRP Publications.

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