The risk coefficients database

The probability of causation (or assigned share) depends on the risk of cancer attributable to radiation exposure. In IREP, the radiation risk for a given cancer is estimated using risk coefficients for cancer incidence developed by the National Cancer Institute (NCI; Land et al., 2002). With few exceptions, the risk coefficients are obtained from the Life Span Studies (LSS) of Japanese atomic bomb survivors from Hiroshima and Nagasaki. The risk coefficients for the incidence of thyroid cancer are obtained from an analysis of a pooled data set that contains information from the Japanese A-bomb survivors and from other studies of medical exposures to X rays (Ron et al., 1995). The risk model for lung cancer from exposure to radon is obtained from an analysis of uranium miners data (RECA, 1996). This document presents a summary of the risk models applied for each cancer type (Table 1), as well as a brief description of the characteristics of each risk model.

The dose–response relationship was found to be linear for all cancer types other than for leukemia and for lung cancer from exposure to radon. The coefficient of the linear dose-response is referred to as the "*ERR/Sv*". The *ERR/Sv* coefficients obtained from analysis of the A-bomb survivors (who were exposed mainly to high doses of gamma radiation delivered at high dose rates) are adjusted when applied for an individual who was chronically exposed to low doses and low dose rates, by using a dose and dose rate reduction factor (DDREF). For leukemia, a linear-quadratic dose response is used for acute exposure to low-LET radiation (see details below). For exposure to radon, the risk of lung cancer is estimated using exposure expressed in working level months (WLM), rather than using radiation dose to the lung tissue (in Sv).

The *ERR/Sv* for each cancer type has an uncertainty obtained from the statistical analysis of the epidemiological data. This type of uncertainty is called "statistical uncertainty," and is given by the profile likelihood function. In some cases, the likelihood function could be described by an analytical probability distribution function (e.g., lognormal). In other cases, the likelihood function was described as a cumulative probability function using a given set of percentiles (ranging from 0.25% to 99.75%). Cubic-spline interpolation between the given percentiles was used to obtain values for any percentile of the cumulative distribution (Press et al., 1992).

The cancer-specific risk models used in IREP can be divided into four broad categories:

1) Group 1 cancers: The *ERR/Sv* depends on both age at exposure and age at time of diagnosis of disease (attained age). For a given age at exposure and attained age, the uncertainty in the ERR/Sv is described by a lognormal distribution with a known geometric mean and geometric standard deviation.

2) Group 2 cancers: The *ERR/Sv* depends on both age at exposure and attained age, but the structure of the model describing this dependency is different from the model for Group 1. For a given age at exposure and attained age, the ERR/Sv is obtained using an age-independent *ERR/Sv* multiplied by an age-dependent modifying factor. The uncertainties in both the age-independent ERR/Sv and in the age-dependent modifying factor are used to obtain the uncertainty in the desired *ERR/Sv*.

3) Group 3 cancers: The *ERR/Sv* for cancers in this group does not depend on age at exposure or attained age. That is, for a given cancer, the *ERR/Sv* and its uncertainty is constant for all ages at exposure and attained ages.

4) Other cancers: Each cancer type in this group has a unique risk model and is treated individually.

Table 1   Risk models used in IREP

Cancer type[a]		Risk model used in calculation	
Name	**ICD-9 code[a]**	**Category**	**ICD-9 code[b]**
Oral Cavity and Pharynx	140-149	Group 2	140-149
Esophagus	150	Group 2	150
Stomach	151	Group 1, 2	151
Colon	153	Group 2	153
Rectum	154	Group 2	154
All digestive	150-159	Group 1	150-159
Liver	155.0	Group 1	155.0
Gallbladder	155.1,156	Group 2	155.1,156
Pancreas	157	Group 2	157
Trachea, bronchus and lung	162	Group 3	162
Other respiratory (nasal cavity, larynx, other)	160, 161, 163-165	Group 2	160, 161, 163-165
Connective tissue	171	Group 2*	170, 171, 175, 190, 194, 195
Non-melanoma (Basal cell carcinoma)	173 (basal cell)	Other cancers	173 (basal cell)
Non-melanoma (Squamous cell carcinoma)	173 (squamous cell)	Other cancers	173 (squamous cell)
Breast-female	174	Group 1	174
Ovary	183	Group 2	183
All female genital (except ovary)	179-182, 184	Group 3	179-182, 184
All male genitalia	185-187	Group 2	185-187
Bladder	188	Group 2	188
Kidney (+etc)	189	Group 2	188-189
Eye	190	Group 2*	170, 171, 175, 190, 194, 195
Nervous system	191, 192	Group 2	191, 192
Thyroid	193	Other cancers	193
Other endocrine glands	194	Group 2*	170, 171, 175, 190, 194, 195
Other and ill-defined sites	195	Group 2*	170, 171, 175, 190, 194, 195
Lymphoma and Multiple Myeloma	200-203	Group 2	200-203
Leukemia (all except chronic lymphocytic)	204-208, less 204.1	Other cancers	204-208, less 204.1
Acute lymphocytic leukemia	204.0	Other cancers	204.0
Acute myelogenous leukemia	205.0	Other cancers	205.0
Chronic myelogenous leukemia	205.1	Other cancers	205.1

[a] Represents the cancer for which the probability of causation is estimated, using the risk models listed in the last two columns.
[b] Represents the cancer types used to derive the risk model from the epidemiological data. The risk models marked in red and with an asterisk (*) are obtained from a set of cancers different from the cancer for which the probability of causation is estimated.

GROUP 1 CANCERS

All digestive cancers (male and female), stomach (female), liver (male and female), and breast (female)

For these cancers, the risk model is described by the following equation:

$$ERR = D \times \alpha \times exp[\beta\ g + \gamma \times min[max(-15,e\text{-}30),0] + \delta \times min(ln(a/50),0)] = D \times ERR/Sv$$

where

- *D* is the radiation equivalent dose (Sv) delivered to the organ responsible for induction of cancer.

- $\alpha, \beta, \gamma, \delta$ are the parameters of the model associated with each modifier.

- *g* is the gender modifier.

- *e* is the age at exposure.

- *a* is the attained age.

The cancer sites in Group 1 have relatively large numbers of cases, exhibit strong evidence of dependencies with age, and strong correlations occur among various model parameters. For these cancers, a lognormal approximation of the *ERR/Sv* was found. In the logarithmic scale, the *ERR/Sv* (at exposure age *e* and attained age *a*) is assumed to be normally distributed with the mean and variance of logarithms defined by the equations below.

$$mean = ln(\alpha) + \gamma \times min[max(-15,e\text{-}30),0] + \delta \times min(ln(a/50),0), \text{ and}$$

$$variance = var(ln\ \alpha)+2 \times cov(ln\ \alpha,\gamma) \times min[max(-15,e\text{-}30),0]+$$
$$2 \times cov(ln\ \alpha,\ \delta) \times min(ln(a/50),0)+var(\gamma) \times min[max(-15,e\text{-}30),0]^2+$$
$$2 \times cov(\gamma,\delta) \times min[max(-15,e\text{-}30),0] \times min(ln(a/50),0)+var(\delta) \times min(ln(a/50),0)^2$$

For a given attained age, the *ERR/Sv* for these cancer types decreases exponentially between ages at exposure of 15 and 30 and is constant outside this interval. Similarly, for a given age at exposure, the *ERR/Sv* decreases linearly with attained age, up to attained age 50, after which it remains constant.

GROUP 2 CANCERS

Oral cavity and pharynx (male and female), esophagus (male and female), stomach (male), colon (male and female), rectum (male and female), gallbladder (male and female), pancreas (male and female), other respiratory except lung (male and female), ovary (female), male genital (male), bladder (male and female), urinary organs less bladder (male and female), nervous system (male and female), lymphoma and multiple myeloma (male and female), other solid cancers (male and female).

The risk model for the cancers in this group is identical to the model for Group 1 cancers. However, these cancers have a relatively lower number of cases, and the α parameters were practically independent of γ and δ. Thus, the *ERR/Sv* (at exposure age *e* and attained age *a*) could be approximated by the following equation:

ERR/Sv(e,a)   =   *ERR/Sv(e=30,a=50)* $\times$ *F(e,a)*

where the age-dependent modifying factor *F(e,a)* is assumed to be independent of the cancer site and is described by a lognormal distribution with a mean of logarithms and a variance of logarithms given by:

mean   =   *-0.05255 $\times$ min[max(-15,e-30),0] - 1.626 $\times$ min[ln(a/50),0]*

variance   =   *0.0003261 $\times$ (min[max(-5,e-30),0])^2*

             -0.007297 $\times$ min[max(-15,e-30),0] $\times$ min[ln(a/50),0]

             + 0.5648 $\times$ {min[ln(a/50),0]}^{2}

In addition to the individual solid tumors listed above, a set of risk coefficients was derived for all other solid tumors as a group. The model for this group of cancers is called the "residual cancers" risk model, and it is applied to estimate the risk from exposure to radiation for the following cancer types: connective tissues, eye, endocrine glands other than thyroid, and ill-defined sites (ICD-9 code = 195). For these cancer types, the data were insufficient to derive individual cancer type models.

GROUP 3 CANCERS

Lung (male and female), female genitalia (less ovary)

The risk model for these cancers shows no age dependency (i.e., $\gamma = \delta = 0$).

ERR   = *D $\times$ ERR/Sv*

The *ERR/Sv* obtained from the epidemiological data for these cancers apply for all ages at exposure and all attained ages.

OTHER CANCERS (GROUP 4)

Non-melanoma of skin (male and female)

The dose-response relationship for non-melanoma skin cancer is based on the most updated Japanese A-bomb survivor cohort data. The only cancer subtype for which a significant dose response was obtained is basal cell skin carcinoma, which is a form of non-melanoma.

The dose-response relationship obtained for basal cell carcinoma shows only an age at exposure dependency. No gender, or attained age dependency was observed.

$$ERR = D \times \alpha \times exp[\gamma \times f(e)] = D \times ERR/Sv$$

where:

$$f(e) = min[max(-30,e-40),0]$$

(i.e. $f(e)$ = -30 for $e \leq$ 10, = e-40 for 10 < e < 40, and = 0 for $e \geq$ 40).

For non-melanoma skin cancers other than basal cell carcinoma (a group of cancers dominated by squamous cell carcinoma), no age dependency could be determined. Thus, a single profile for *ERR/Sv* is applied for all ages at exposures, all attained ages and both genders.

Thyroid

The dose-response relationship for thyroid cancer was obtained by re-analyzing the pooled data of seven studies which include the studies of Japanese A-bomb survivors and of patients exposed to X rays (Ron et al., 1995). The dose-response from this analysis shows a strong dependency on age at exposure (*e*), and includes exposures in adulthood. No statistically significant gender-dependency was determined. The *ERR/Sv* for different ages at exposure (*e*) can be described by a lognormal distribution with the geometric mean (*GM*) and geometric standard deviation (*GSD*) provided in Table 2.

Leukemia

The dose-response relationship for leukemia is based on all cases of leukemia observed in the Japanese A-bomb survivor cohort, other than chronic lymphocytic leukemia (CLL). No association between radiation and CLL has been identified to date. The risk of leukemia per unit dose (*ERR/Sv*) decreases with age at exposure and with time since exposure. A linear quadratic dose-response is used to estimate risk from exposure to acute low-LET doses of radiation.

$$ERR = (ERR/Sv) \times (D+D^2);$$ where *D* is the radiation dose equivalent in Sv.

Table 2   *ERR/Sv coefficients for thyroid cancer*

Age at exposure	Geometric mean	Geometric standard deviation
0	9.463	2.183
5	6.262	1.924
10	4.136	1.976
15	2.732	2.160
20	1.804	2.301
25	1.192	2.367
30	0.788	2.365
35	0.521	2.379
40	0.345	2.732
45	0.228	3.140
50	0.151	3.611

A linear dose response is used in all other exposure situations (i.e., high-LET and low-LET radiation delivered at low dose rates).

$$ERR = (ERR/Sv) \times D; \text{ where } D \text{ is the radiation equivalent dose (Sv).}$$

The *ERR/Sv* is the same for both types of dose response and depends on age at exposure (*e*) and time after exposure (*t*). No gender dependency was determined for leukemia.

$$ERR/Sv = exp(ln(\alpha)+\gamma \times e +\varepsilon \times t)$$

The model parameters α, γ, and ε are obtained from statistical analysis of the data. The parameter α corresponds to the excess relative risk for age at exposure $e=0$, and time since exposure $t=0$, given that $D + D^2 = 1$ (for acute exposures to low-LET radiation), or the dose is $D = 1$ Sv (for all other exposure situations).

In addition to all types of leukemia as a group, individual types of leukemia were studied by using the same dose response model.

Acute Myeloid Leukemia (AML)

The risk of Acute Myeloid Leukemia from exposure to radiation was found to decrease exponentially with time after exposure (*t*). No dependency of the risk on age at exposure (e; $\gamma = 0$) or gender was observed for AML in the A-bomb survivor cohort.

Chronic Myeloid Leukemia (CML)

The risk of Chronic Myeloid Leukemia from exposure to radiation decreases exponentially with time after exposure (*t*). The risk for males decreases faster than the risk for females. No dependency on age at exposure (e; $\gamma = 0$) was determined for CML.

Acute Lymphocytic Leukemia (ALL)

The risk of Acute Lymphocytic Leukemia from exposure to radiation decreases exponentially with time since exposure (*t*) when exposure occurs before age 20. No time-since-exposure dependency was identified for exposure in adulthood. Also, no gender dependency was determined for ALL.

Lung cancer from exposure to radon

The risk from exposure to radon is derived from studies of uranium miners (RECA, 1996). The risk model depends on the level of exposure to radon (expressed in working level months – WLM) rather than on radiation dose to the lung tissues.

$$ERR = \alpha \times WLM^{0.8194}$$

where *WLM* is the number of working level months from exposure to radon provided by the user. The coefficient α represents the risk from exposure to 1 WLM. Alpha was found to decrease exponentially with the attained age (*a*) for $45 \leq a \leq 75$ and with the time since last exposure (TSLE) for 5 years $\leq$ TSLE $\leq$ 25 years. Outside these limits, α is constant and equal to the α at the respective limit.

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