Written amendment to 23 September memo, provided by Charles Land to NAS committee on 19 December, 1997

Calculation of the Estimated Lifetime Risk of Radiation-Related Thyroid Cancer in the U.S. Population from NTS Fallout

1. Thyroid cancer risk associated with gamma-ray and x-ray exposure, from studies of the Hiroshima-Nagasaki survivors and of various medically-exposed populations, is well quantified. Findings are summarized in a pooled analysis of seven studies (Ron et al., Radiation Research 1995; 141:259-277).
   - The evidence for a radiation-related risk is strong for childhood exposure, and weak or non-existent for adult exposure.
   - Dose-specific excess risk decreases with increasing age at exposure. At ages 5-9, it is about half that associated with exposure at ages 0-4, and at 10-14 it is about half that at 5-9.
   - For any given exposure age, excess risk appears to be proportional to thyroid dose (linear dose response).
   - Ron et al. estimated an excess relative risk (ERR) of 7.7 per Gy, or 0.077 per rad, for childhood exposure at ages younger than 15.
2. The average (case-weighted) exposure age in the pooled data was a little over $4^1/_2$ years. By linear interpolation between the midpoints of the first two intervals, and extension of the observed reduction in ERR with increasing age at exposure, the following age-specific coefficients were inferred:

Age at exposure	ERR at 1 rad
0-4	0.098
5-9	0.049
10-14	0.0245
≥ 20	negligible

3. Although there was evidence of variation radiation-related relative risk over time following exposure, there was no evidence of a trend. Accordingly, ERR was assumed to remain constant over the remainder of life.
4. Data on risk associated with thyroid exposure from ingested or inhaled ^{131}I suggest that there is a risk, but precise dose-response estimates are not available. Accordingly, it is reasonable to use the coefficients developed from data on x-ray and gamma-ray exposure, with an appropriate value for the relative biological effectiveness of ^{131}I compared to gamma rays or x rays.
   - NCRP report No. 80, "Induction of Thyroid Cancer by Ionizing Radiation," 1985, gave a range of 0.1 to 1.0 for the RBE, based on experimental studies. The report recommended 0.3 for radiation protection purposes, as the highest credible value. The NCRP report also stated that the RBE of

^{131}I relative to x ray may be lower at high doses and dose rates, and higher (nearer to x ray in effectiveness) at low doses and dose rates.

- Thus, Walinder (1972, summarized in the NCRP report) obtained an RBE of 0.1 using ^{131}I thyroid doses in the range 2200-11,000 rad, whereas
- Lee et al. (1982) found near equivalence using dose groups at 80, 330, and 850 rad.
- Laird (1987) conducted parallel and combined analyses of 6 cohorts of children exposed to external radiation and one exposed to ^{131}I, and re-evaluated experimental data from the large study by Lee et al. (1982) specifically designed to investigate the RBE of ^{131}I. Her RBE estimate was 0.66 with 95% confidence limits 0.14-3.15 (however, there is no support that I know of for an RBE greater than 1).
- The RBE value at low doses remains a contentious issue.
- In the calculations for NCI, RBE values of 1, 0.66, 0.33, and 0.1 were assumed.

5. In addition to being more sensitive to the carcinogenic effects of ionizing radiation, the thyroid glands of children receive higher doses from ingested or inhaled ^{131}I than do the glands of adults, because of smaller gland size, higher intake of milk, and higher metabolism. Using conversion factors obtained from Dr. Bouville, the estimated average thyroid dose of 2 rad to the U.S. population from Nevada Test Site fallout was converted to the following values for children:

Exposure Age	Estimated Average Dose
<1	10.3
1-4	6.7
5-9	4.5
10-14	2.8
15-19	1.8

6. Lifetime cumulative thyroid cancer incidence rates of 0.25% for males and 0.64% for females, respectively, were assumed, based on the SEER report for 1973-1992. The 1973-1994 SEER volume is now out, and gives 0.27% for males and 0.66% for females. Use of the new values would increase the total by about 4%.

7. For simplicity of calculation, it was assumed that the U.S. population in 1952 received the total thyroid dose from NTS fallout in that year, instead of spread out over 12 years. This simplification was possible because, using a linear dose-response model, lifetime radiation-related thyroid cancer risk is proportional to summed collective dose, in person-rads, over exposure ages weighted by age-specific risk coefficient.

8. For each single year of age (column 1 in the spreadsheet), the sex-specific estimated numbers of lifetime excess thyroid cancer cases in the US due to NTS fallout (columns 8 and 9) were obtained as the product of:
   - the number of male or female persons in the 1952 US population (columns 2 and 3)
   - the age-specific estimated average cumulative thyroid dose over the entire period of above-ground testing (column 4)
   - the age-specific linear dose-response coefficient (ERR at 1 rad) for x ray and gamma ray (column 5), times the assumed RBE for ^{131}I
   - the cumulative lifetime thyroid cancer risk for men or women (0.25% or 0.64%), as appropriate.
9. The age and sex-specific totals were summed over sexes (column 10) and ages. The sums are given below columns 8-10 in each table.
10. Besides uncertainty about the RBE, there is also statistical uncertainty about the risk coefficients, and subjective and statistical uncertainty about the average doses used. The combined uncertainty is substantial. For example:
    - 95% confidence limits (2.1-28.7) for the Ron estimate of $ERR_{1Gy} = 7.7$ correspond approximately to a lognormal model geometric standard deviation (GSD) of about 1.95.
    - The uncertainty of average dose estimated by the NCI, 2 rad, was stated to be between 1 and 4, i.e., a factor of 2 in each direction. This corresponds approximately to 95% confidence limits and thus to a GSD of about 1.4.
    - Therefore, the product of that dose and the estimated ERR at 1 rad has a GSD of 2.1 (calculated as the exponential of the square root of the sum of squares of the natural logarithms of 1.95 and 1.4).
    - Approximate 95% confidence limits for the number of excess cases can be obtained by dividing and multiplying by 4.3 ($=2.1^{1.96}$). Thus, for example, ignoring all other possible sources of error, an estimate of 49,000 lifetime excess cases (corresponding to a fixed RBE of 0.66, which here is assumed to be known without error) might be given with uncertainty 11,300-212,000.