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The Evolution of Risk Cross Section

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Introduction

In the NASA Space Radiation Cancer Risk models 2010 and 2012 (NASA, 2011, 2013), the concept of a *risk cross section* was introduced to relate the cancer risk directly to the physical quantity of the charged particle fluence appearing in the organs of a space traveler. Since this approach is a modification of the conventional way of relating the absorbed dose to the risk through a quality factor, it is of interest to examine how this quantity relates to the conventional approach and how it evolved from earlier ideas of risk/fluence.

The idea of a "cross section" comes originally from the field of Nuclear Physics, where experimental results are commonly reported in terms of scattering and nuclear cross sections. Historically, beams of charged particles were directed at targets, and detectors measured the nuclear products resulting from collisions of the particles with the target atoms. It was convenient to describe the experimental results in terms of the probability of a particular product being produced or interaction occurring per unit fluence of incoming beam. Fluence is the number of particles in the incident beam per unit area. So the experimental results have the units of number of detected events/(particles/unit area). The result is a probability of event per unit fluence, which has the units of an area because the area rises to the numerator. This is the reason the quantity is called a "cross section". So as used in Physics or Biology, a cross section is not a physical property of the target, but is more correctly a *probability per unit fluence* for a particular endpoint to occur. In biology, this endpoint is an experimental endpoint (cell inactivation, mutation, etc.) and the resulting quantity is often referred to as an *action cross section*.

Risk cross section is an extension of this idea. In a radiation environment, it is the probability per unit fluence of an untoward event or disease occurring, for example, lung cancer, leukemia, etc. In the space risk analysis field, the fluence is the fluence of cosmic ray particles (and their nuclear secondaries) found in the body of a space traveler, appropriately averaged over an organ of interest such as the lung or the blood-forming organs. The risk cross section for lung cancer incidence, for instance, is the probability per unit fluence for lung cancer to occur in a space traveler behind a given shielding configuration for a specified mission duration. It should be emphasized here that this concept is well defined at low fluences only, where biological effects are expected from traversals of *single* heavy charged particle tracks through cells. This is the case expected for exposure to Galactic Cosmic Rays (GCR) on extended space flight. (See, for instance, the referenced article for Curtis, S.B., 2013, and Curtis and Letaw, 1989).

Evolution of the Concept

The concept of risk cross section grew initially out of the idea of Fractional Cell Lethality (FCL), developed to calculate the fraction of cells killed at points within an astronaut exposed to solar particle radiation in several large solar particle events (Curtis et al., 1966). Cell inactivation cross sections as a function of LET were developed from experimental data of cell survival from human cells irradiated in charged particle beams (Barendsen et al., 1963, Todd, 1965). These functions of survival (probabilities of cell survival per unit fluence) vs. LET were multiplied by the fluence-LET spectra of three major components of the solar particle spectra

[protons, helium ions and M ions, the latter assumed to be oxygen (z=8) ions] at two points within an astronaut's body for two solar particle events. The results showed that between 1 and 7 percent of the astronaut's cells would be killed at 4 or 6 cm depth within an astronaut's body depending on the solar particle event and the available shielding. There was no consideration of a DDREF (dose and dose rate effectiveness factor) in this analysis (see the article on DDREF in THREE for more on this factor).

Somewhat later the idea of cross section was used in the IGK model developed by Katz and his co-workers in calculating cell survival (Katz et al, 1971), but was not utilized in space risk analysis. In 1985 another fluence-related idea, the hit-size effectiveness function (HSEF), was suggested (Bond et al., 1985).

Introduction of Risk Cross Section into Space Risk Analysis

The concept risk cross section was introduced at a NATO Advanced Study Institute "Biological Effects of Solar and Galactic Cosmic Radiation" in Portugal in 1991 (Curtis, 1993). It was pointed out that there was a way of defining risk without having to estimate the dose equivalent or equivalent dose by using the concept of *risk cross section*, originally called a fluence-related risk coefficient (Curtis et al., 1992). When the probabilities of effect (e.g., carcinogenesis) are small compared to unity for each radiation track traversal, and the fluences are low so that the effect can be considered as arising from single track traversals, the risk cross sections, $\Sigma(L_i)$, can be added, and the risk, R, becomes:

$$R = \sum_{i=1}^{n} \int \Sigma(L_i) F_i(L_i) dL_i \qquad (1)$$

Here the summation is over the different particle species (i) in the total fluence-LET spectrum, $F_i(L_i)$, of each particle over the mission length and the integral is over the differential LET spectra of each of the particles, L_i. Alternatively, the integrations can be over the fluence-energy spectra, $F_i(E_i)$, to directly relate the risk to the field quantities of transport theory (Wilson et al., 1987). In that case, there will be a $\Sigma_i(E_i)$ for each particle type and energy.

Relationship with the Conventional Method of Determining Risk from Mixed Radiation Environments

The conventional way of calculating risk has been to use a Quality Factor, Q, which is a weighting factor that is a function of the LET of the particle and whose LET dependence has traditionally been set by the International Commission on Radiological Protection (see for instance ICRP, 1991). The dose equivalent, H, is found by multiplying the Quality Factor, $Q(L_i)$, by the *dose* distribution, $D_i(L_i)$, from the ith particle at the point in question in the astronaut's body and integrating over the LET for each particle type, i, in the radiation environment and adding the contributions from each particle. Mathematically, we have:

$$H = \sum_{i=1}^{n} \int Q(L_i) D_i(L_i) dL_i \qquad (2)$$

Then multiplying by the risk coefficient for low LET radiation, α_γ, we have:

$$R = \alpha_\gamma H = \alpha_\gamma \sum_{i=1}^{n} \int Q(L_i) D_i(L_i) dL_i \qquad (3)$$

We can now bring the α_γ inside the summation and integral signs, and from equations (1) and (3), we notice that the integrands can be equated:

$$\Sigma(L_i) F_i(L_i) = \alpha_\gamma Q(L_i) D_i(L_i) \qquad (4)$$

The dose distribution and fluence distribution are related by $D(L) = k_1 L F(L)$, so we see that the relation between the two can be written:

$$\Sigma(L_i)F_i(L_i) = \alpha_\gamma k_1 Q(L_i) L_i F_i(L_i) \quad (5)$$

so that a "conventional" risk cross section can be defined in terms of the legislated values of quality factor yielding:

$$\Sigma_c(L) = \alpha_\gamma k_1 Q(L) L \quad (6)$$

where we have dropped the subscript *i*. The quality factor is a universal function of *L*, i.e., independent of particle species. The value of this cross section for low LET radiation [*Q(L)* = 1, α_γ = 0.04/Gy and *L* = 0.24 keV/μm] is 1.5 x 10^{-3} μm^2. The value of k_1 is 1/6.24 for these units of fluence, dose and LET in equations (5) and (6).

For a detailed discussion of the *conventional risk cross section* see Curtis, 1994a, and for calculations using it to estimate risks in radiation-sensitive and cancer-prone organs from galactic cosmic rays, see Curtis et al., 1995.

The First Risk Cross Section: a Function of LET

As an example of the use of the concept, the first risk cross section function was chosen in a study to predict the prevalence of Harderian gland tumors in B6CF1 mice exposed to a typical GCR spectrum for a year in space at Solar Minimum behind a spherical shielding thickness of 1 g/cm^2 aluminum (Curtis et al., 1992). This endpoint was used as a numerical example because data were available at the time to which to apply the model. Experimentally determined tumor prevalence cross sections were used from noting the *initial slope* of the prevalence vs. fluence curves for mice irradiated in high energy heavy ion beams at the Berkeley Bevalac (Fry et al., 1985).

The fluence, *F*, and dose, *D*, are related by the expression:

$$F = 6.24\, D/L \quad (7)$$

where F, the fluence, is in number of particles per square micrometer, D, the dose, is in Gy and L, the LET, is in keV/μm (the stopping medium assumed here is water).

The initial expression was not obtained from a biological model, but was simply chosen to provide (1) a region at low LET where the cross section increases linearly with LET, (2) a region where it increases more rapidly and (3) a region of saturation at high LET, picked here to be at the point of the iron beam results (193 keV/μm). The expression chosen for the early risk cross section (in μm^2) was:

$$\Sigma(L) = 9.9 \times 10^{-3} L + 195\left[1 + \exp\left(-\frac{L}{14}\right)\right][1 - \exp(-7.43 \times 10^{-6} L^2 - 1.14 \times 10^{-8} L^3)]$$

$L < 193\ keV/\mu m$

$$= 60.9 \qquad L \geq 193\ keV/\mu m \quad (8)$$

This expression is shown in Fig. 1 along with the conventional risk cross section of Eq. (6) with α_γ = 4%/Gy.

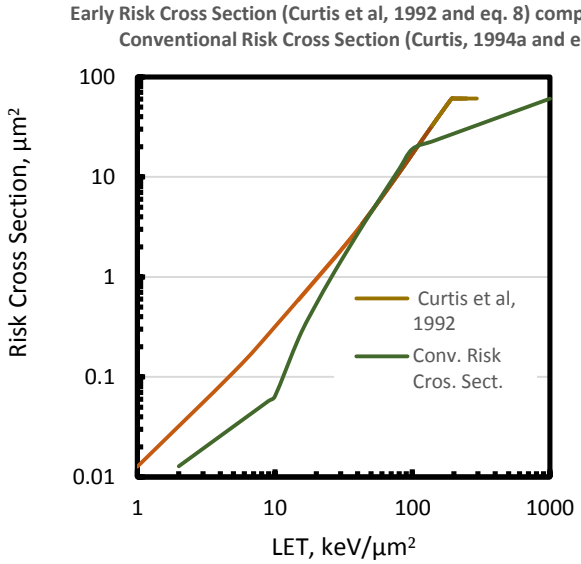

Figure 1. The risk cross section first developed by Curtis et al., 1992 (eq. 8), to describe the Harderian gland tumorigenesis results of Fry et al., 1985, compared to the conventional risk cross section (eq. 6).

Contribution from Target Fragmentation

Even at this early stage of concept formulation, it was recognized that there would be a small contribution from the fragmentation of nuclei of the biological tissue (the "target" nuclei) by the high energy primary (and secondary) ions of the cosmic rays, particularly from the low-z component (protons and helium ions) that should not be neglected (Shinn et al., 1990). So the risk cross section was written:

$$\Sigma_i(L_i) = \Sigma(L_i) + \Sigma_i(targ\ frag)_i \qquad (9)$$

Prevalence per Year in Space Flight Outside the Magnetosphere at Solar Minimum

The risk cross sections were used to estimate the yearly prevalence of Harderian gland tumors in B6CF1 mice in space outside the magnetosphere at Solar Minimum behind 1 g/cm^2 spherical aluminum shielding; the mouse geometry was ignored. The results are shown in Table I, both excluding and including target fragmentation (eq. 9). Protons (z=1) contribute some 15% and helium ions (z=2) around 6.5% to the total prevalence. Two conclusions from this calculation are that target fragments make only a small contribution to the total prevalence and predominantly only for the low z groups, and a large contribution to the prevalence comes from the higher z groups with more than half from the charge group between 10 and 28.

Table I. Prevalence of Harderian gland tumors per year

	Direct Ionization	Including target fragmentation
1	**0.0052**	**0.0092**
2	**0.0029**	**0.0039**
3 – 9	**0.0089**	**0.0101**
10 – 28	**0.0362**	**0.0367**
Total	**0.0532**	**0.0599**

Track Structure Considerations

Even in early consideration of the radiation quality of high LET particles, it was recognized that for several biological endpoints, e.g., the oxygen enhancement ratio (OER) (Curtis, 1970) and cell survival (Katz, 1970, Katz et al., 1971), LET might not be the best descriptor of radiation quality. The physics of energy deposition as a charged particle slows down suggests that the *track structure* inherent in each charged particle species (i.e., the pattern of energy deposition from the delta rays) might dictate the response of a biological system. [1]Suffice it to say here that experimental evidence has shown that for several important biological endpoints, the quantity z^{*2}/β^2 [where z* is the effective charge of the particle, taking electron pickup (capture) into account at low velocity, and β is the ratio of the particle velocity to that of light in vacuum] is more accurate and appears to have advantages over LET as a quantity to specify biological response for the particle fluences and energies important in space radiation risk analysis. This quantity is proportional to the number of electrons emitted per unit length by the ionization process as the particle slows down.

One suggestion for the dependence of risk cross section on z^{*2}/β^2 was developed in a report titled *Fluence-based and Microdosimetric Event-based Methods for Radiation Protection in Space* by the National Council on Radiation Protection (NCRP, 2001). Here the functional form chosen included a term rising linearly with z^{*2}/β^2 before decreasing at higher values, and another term increasing rapidly at higher values of z^{*2}/β^2 and soon dominating until leveling off (representing saturation) at high values. The expression used was

$$\Sigma(\xi) = \sigma_1\{1 - [e^{-a\xi}(1 + a\xi)]^n\} + \sigma_2 a\xi e^{-a\xi} \qquad (10)$$

where $\xi = z^{*2}/\beta^2$ and four constants have the values: $\sigma_1 = 20\ \mu m^2, a = 4 \times 10^{-4}, \sigma_2 = 3\ \mu m^2$, and $n = 10$. The expression is shown in Figure 2. The constant, σ_2, in the second term which dominates at low LET, was adjusted to give a value of $1.5 \times 10^{-3}\ \mu m^2$ for the cross section at 0.24 kev/μm (see above). The Harderian gland tumorigenesis mouse data (Alpen et al., 1994) was anchored at this "gamma ray" data point ($z^{*2}/\beta^2 = 1$). The value of σ_1 was then adjusted to saturate the curve close to the data where they fell at high LET.

[1] A detailed article covering track structure and its role in determining biological effect is in preparation.

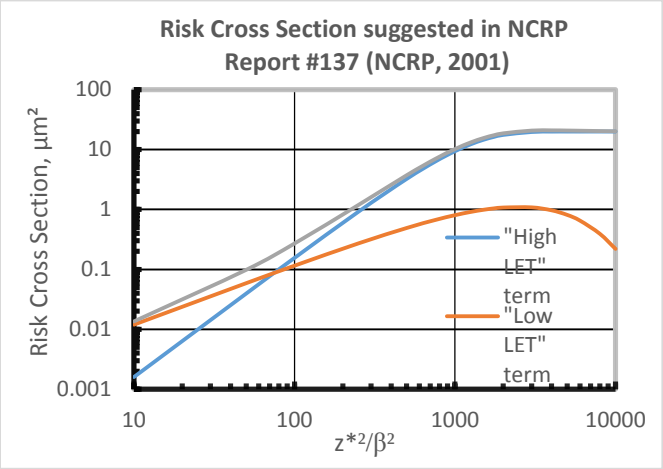

Figure 2. Risk Cross Section as a function of z^{*2}/β^2 suggested in NCRP Report #137 (See complete attribution in the Figure 3 legend). Here the two components, "High LET" and "Low LET" denote the two terms involving σ_1 and σ_2 in equation (10), respectively.

The functional form was not chosen from a specific radiation carcinogenic model, but arises in the LPL model of cell inactivation (for derivation, see Curtis 1986). It was convenient to use since it has a term dominating at high LET with constant σ_1, and another term with constant σ_2 dominating at low LET.

Because this functional form of the cross section depends only on z^{*2}/β^2, it breaks into a family of curves for the different particle species of heavy ions when plotted as a function of LET. Figure 3 presents these curves for various components of the GCR, and compares them to the experimental mouse Harderian gland tumor data. Target fragmentation contributions from protons and helium ions are included (NCRP 2001).

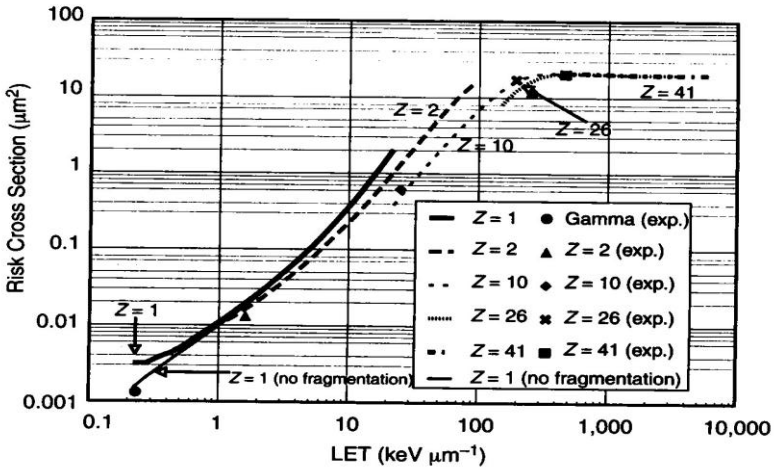

Figure 3. Risk cross sections as a function of LET for five particles (protons, helium ions, neon ions, iron ions, and niobium ions) plotted with the Harderian gland tumorigenesis data normalized with the low-LET point (gamma rays) at 0.24 keV/μm. The target

fragmentation-corrected curves for protons and helium ions (z=1 and 2) are shown. [NCRP, 2001., Reprinted with permission of the National Council on Radiation Protection and Measurements, http://NCRPpublications.org). Cindy L. O'Brien NCRP Managing Editor 7910 Woodmont Avenue, Suite 400 Bethesda, MD 20814-3095 Voice: 301.657.2652 x15 Fax: 301.907.8768]

Inclusion of Risk Cross Section in the NASA Space Radiation Cancer Risk Model

The risk cross section concept has been incorporated into the NASA Space Cancer Risk Models 2010 and 2012 (NASA, 2011, 2013). The expression for the cross section assumed in this model is given in the following two expressions:

$$\Sigma(z,\beta,L) = \Sigma_{\mathrm{o}} P(z,\beta) + \frac{\alpha_{\gamma} L}{6.24}[1 - P(z,\beta)] \qquad (11)$$

with

$$P(z,\beta) = [1 - \exp(-z^{*2}/\kappa\beta^2)]^{\mathrm{m}} \qquad (12)$$

It was obtained from considerations coming from the Katz model of cell killing (Katz et al., 1971) and subsequent ideas developed by Wilson and Cucinotta (Wilson et al, 1993, Cucinotta and Wilson, 1995). The parameters, Σ_0, m and κ are based on subjective estimates from radiobiology experiments, and the low-LET slope, α_γ, estimated from human epidemiology data for γ-rays. We note that the second term of eq. 11 (the low LET term) shows a linear relationship with LET at low LET.

The parameterization for subsequent calculations of uncertainties is defined in terms of the ratio of the risk cross section to the low-LET low-dose risk coefficient, α_γ, so only the value of Σ/α_γ is needed. This means that a parameter value ratio of Σ_0/α_γ is necessary. The parameter values chosen in the NASA model are shown in Table II.

Table II. Parameters for the NASA Risk Cross Sections for solid tumor and leukemia risks* (From NASA, 2013)

Parameter	Solid Cancer	Leukemia
m	3	3
κ	550 (1000)	550 (1000)
Σ_0/α_γ (in μm^2 Gy)	7000/6.24	1750/6.24

*Values for κ in parentheses are for light ions (z<5).

As is reflected in Table II, two factors, not considered in the earlier work described above, were included in the NASA risk model: (1) giving a separate parameter value of Σ_0/α_γ for leukemia, and (2) giving separate values of the parameter κ for light particles with z<5. This change in the value of κ for light ions is to provide for the peak RBE (called Q_{max} in the NASA risk model) for protons and He ions to occur in the model at their experimentally found values of energy. An additional term for non-targeted effects was also included in the model but will not be discussed here.

Using the values in Table II for solid tumors and the heavy ion (i.e., $z \geq 5$) component, risk cross sections scaled by α_γ^{-1} as a function of LET are shown in Figure 4 for ^{12}C, ^{20}Ne, ^{28}Si, ^{40}Ca and ^{56}Fe ions.

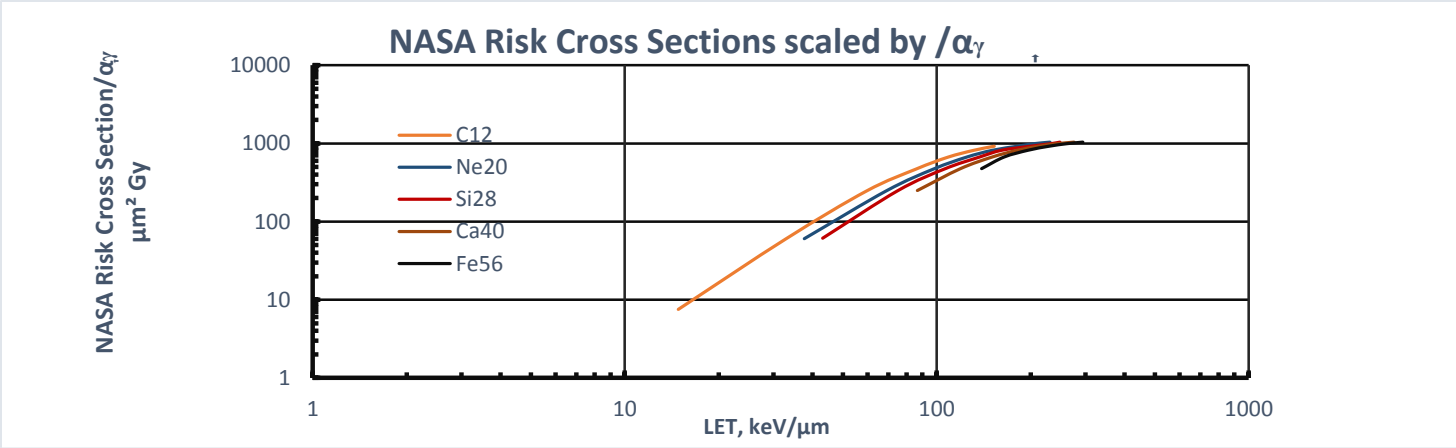

Figure 4. NASA solid tumor risk cross sections scaled by α_γ^{-1} as a function of LET. The multivalued nature of the curves is clearly seen at lower LET.

Concluding Remarks

For the 2012 NASA Radiation Cancer Risk Model (NASA 2013), the risk for each cancer from each radiation component is obtained, then multiplied by an appropriate low-LET risk coefficient (i.e., dividing by a DDREF; the present value NASA has chosen is 1.5 for all solid cancers) for that cancer and added to obtain the total increased risk of cancer incidence [denoted REIC (risk of exposure-induced cancer)] or death [denoted REID (risk of exposure-induced death)]. If the total dose rate (or fluence rate) from each GCR component is such that the interaction between biological lesions caused by different track traversals is negligible, it is reasonable to accept the additivity assumption that the above summations and integrations imply. It has been pointed out, however, that if the exposure is protracted over many cell population doubling times (as will be the case on extended space missions of the future), it is possible that cells may acquire non-lethal pre-neoplastic lesions (e.g., genomic instability) and proliferate to increase the number of "initiated" cells via clonal expansion for increased susceptibility to later radiation-induced carcinogenic events (Curtis 1994b, 1996). If so, the strict additivity inherent in the integrations and summations implied above would not be appropriate. Even if appropriate for the very low fluence rates found in the space radiation environment, these rates must also be low enough in the laboratory so that such interactions between lesions from separate tracks are negligible (Curtis 1994b). One indication that a *protraction effect* is occurring, at least for high-LET radiation, has been seen in a study of a group of Colorado Plateau miners who inhaled alpha-particle emitting radon daughters leading to a distinct protraction effect (Luebeck et al., 1999). That is, there is an increased risk of lung cancer from a protracted exposure to radon daughters over that from a shorter exposure to the same total dose. It has been suggested that radiation-induced initiation (one or more mutations occurring in irradiated cells) may not be as important as radiation-induced modification of cell proliferation kinetics in already initiated cells (Curtis et al., 2001). In the model, this protraction is due to a strong effect of the radiation on the *promotion* term (proliferation rate of initiated cells). Such an effect, if important in the high-LET environment found in space, should be incorporated into the risk cross section model as a fluence-rate dependent factor.

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