A BASIC MODEL OF RISK CONTROL IN HEALTH PHYSICS

Shigeru KUMAZAWA

Senior Expert[*1] of Health Physics, Formally JAERI/ USEPA/ JNES/ NSC

ABSTRACT: This paper is to raise a question "What is the numerical nature of risk control in life phenomena?" in order to make a systematic description of dose-response relationship as a simple form of risk assessment. According to the analysis of occupational individual dose distributions, the law of proportionate effect and the feedback against the excess adverse effect might be the fundamentals of risk control. Suppose there is the same nature of risk control in biological systems as well as in radiation protection, it is suggested that the hybrid scale model developed in Health Physics might be applied to some data of the biological experiments and the human epidemiology.

INTRODUTION

In the modern society we are facing various types of risks in life. The ionizing radiation is one of risks for us with the dependence on dose and dose rate. Over about one hundred and twenty years, we have acquired how reasonably to cope with individual doses to workers at jobs required, daily or in life time. As we analyze the distribution of individual doses incurred by workers among an occupational group in the system of radiation protection, it leads to the special characteristics of dose distribution reasonably attained in a balance between dose increase required for net benefit in life and dose reduction to maintain the quality of life in terms of radiological matter relating to our knowledge of radiation effects.

The 1977 Recommendations of the International Commission on Radiological Protection (ICRP) [(1)] first stated "the distribution of the annual dose equivalents in large occupational groups has been shown very commonly to fit a lognormal function, with an arithmetic mean of about 5 mSv, and with very few values approaching the limit" of 50 mSv (paragraph 100, ICRP Pub. 26). The dose limit 50 mSv had been derived so that the average annual mortality due to occupational radiation hazards should not exceed 10^{-4} as a safety industry. Later, the 1982 Report of the United Nations Scientific Committee on the Atomic Radiation (UNSCEAR) [(2)] reviewed it as "The hybrid log-normal (*suggested by Kumazawa and Numakunai* [(3, 4)] *as a combination of log-normal and normal distribution*) is derived from the log-normal by including a feedback mechanism which relates control of future doses to the previous cumulative dose. As this includes constraint functions which appears to apply rather generally it is probably a better way to represent observed distribution" (paragraphs 20, 32, Annex H).

The hybrid log-normal (HLN) distribution is defined as the probability distribution of X whose transformation $\rho X + \ln \rho X$ follows the normal distribution with the mean μ and the variance σ^2 of the transformation. The genesis of the HLN distribution was proved according to the stochastic process of dose accumulation with a feedback mechanism of dose constraint via the Martingale central limiting theorem [(4)]. The hybrid function $\mathrm{hyb}(x) = x + \ln(x)$ is the key concept to balance between dose increase and dose constraint. This paper discussed a feasibility of the hybrid function to formulate various dose-response relationships.

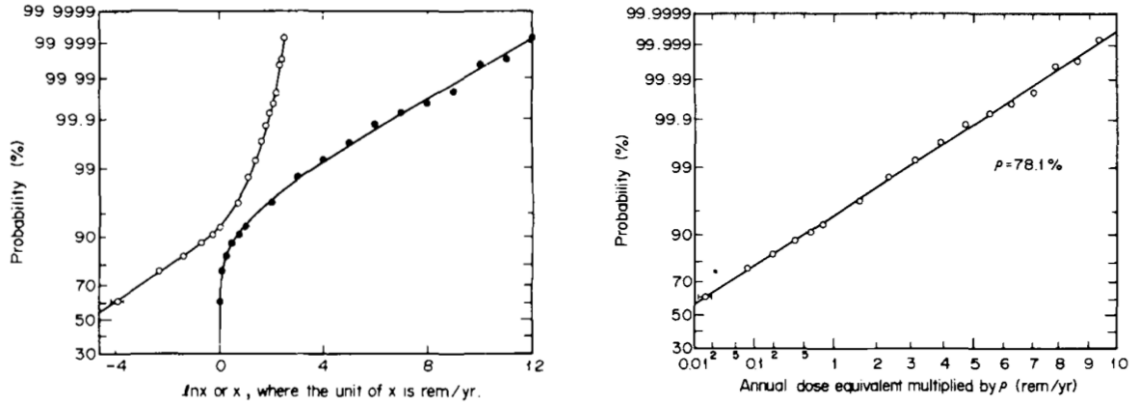
BACKGROUND

The distribution of doses to ionizing radiation often deviates from the log-normal model at the higher dose due to an "as low as reasonably achievable" (ALARA) program in the system of radiation protection. In 1980 the hybrid log-normal model, which unifies the log-normal and the normal models, was developed at the Japan Atomic Energy Research Institute to include the feedback reduction of dose increasing on the law of proportionate effect over the job according to the degree of radiation exposure.

The HLN distribution is defined for a variate X whose function $\mathrm{hyb}\,(\rho X) = \rho X + \ln \rho X$ is normally distributed. The dose increment ΔX is randomly proportionate to the previous cumulative dose X the magnitude of which might correspond to a predictive dose as a product of dose rate and time at work: $\Delta X = \varepsilon X$ or $\Delta \ln X = \varepsilon$ where ε is a random coefficient of exposure stimulus. For the large value of ΔX, the dose reduction effort works as $\Delta X = (\varepsilon - \rho \Delta X)\, X$ via a feedback mechanism with an overall feedback factor ρ and it results in $\Delta X = \varepsilon\, X/(1 + \rho X)$ or $\Delta(\rho X + \ln \rho X) = \varepsilon$, namely $\Delta\,\mathrm{hyb}\,(\rho\, X) = \varepsilon$.

Suppose the exposure process for a given period (0, *T*) can be divided by n as many hypothetical steps as we want, the sum $A_n(t) = \sum_{i=1}^{[nt/T]} \varepsilon_i$, the limiting distribution of which becomes to be normally distributed according to the Martingale central limit theorems, converges to $\int_{X_0}^{X_T} d\,\mathrm{hyb}\,\rho X = \mathrm{hyb}\,\rho X_T - \mathrm{hyb}\,\rho X_0$ where X_T is the cumulative dose at time *T*. Thus $\mathrm{hyb}\,\rho X_T$ becomes to be normally distributed and X_T becomes to be hybrid log-normally distributed. The first application was Fig.1 (Kumazawa and Numakunai, 1981). The shape of the distribution of X_T changes from log-normal to normal via the HLN expression according to the increase in the feedback factor from ρ = 0 to +∞ according to constraining exposure.

This generic model is satisfactory as a basic dose distribution model as it confirms the adequacy of the ICRP log-normal model for low doses controlled be weak constraints. It affords a theoretical basis for the exposure control process leading to the HLN model and the possible law of proportionate constraint to control radiation risk.



(a) Normal (●) and Log-Normal (○) plots (b) Hybrid Log-Normal plots

Fig. 1 Annual doses to workers at the licensed facilities of NRC in the United States, 1974 [3].

CELL SURVIVAL CURVES

The cellular radiation damage and repair has been studied significantly as the following findings [5]: (a) the cells have repair systems to which the enzymes is important to guard the cellular checkpoints and carry out

the repair. (b) The cells have a programmed death system (apoptosis) that can take out and kill the most damaged cells. (c) Adaptive response has been observed that small doses of radiation given before a large challenge dose prepare or trig the repair processes with the result that the radiation damage is reduced. (d) The Oslo group has found that small radiation doses, given at a low dose rate, release the TGFWβ3 factor that is important with regard to repair processes, that is the possibility of interpretation that radiation might be a necessity for life.

The cellular repair processes mentioned above can reduce the cell inactivation coefficient λ to λ', depending on the magnitude of the surviving fraction S during repairing the sublethal damages to dose D. Analogous to the HLN model of radiation dose control, putting the reduced inactivation coefficient $\lambda' = \lambda - \rho\,(-dS/dD)$ in $dS/dD = -\lambda' S$, where ρ is the feedback factor corresponding to the overall effectiveness of cellular repair processes, we obtain $dS/dD = -\lambda\, S/(1+\rho\, S)$. Thus the cellular repair processes seems to result in $\mathbf{hyb}\,(\boldsymbol{\rho S}) = \boldsymbol{\delta - \lambda D}$ where $\delta = \text{hyb}\,(\rho)$ due to S = 1 at D = 0. This equation is called the hybrid scale (HS) model of cell survival. For ρ > 0 with somewhat the effectiveness of cellular repair processes, the cell survival curve has the shoulder on a semi-logarithmic plot and for ρ= 0 without the effectiveness of those, the cell survival curve is straight on the same plot because of $\mathbf{ln}\, \boldsymbol{S = -\lambda D}$ or $dS/dD = -\lambda\, S/(1+\rho\, S) = -\lambda\, S$.

To verify the applicability of the HS model of cell survival to experimental data, we used the historical data (Elkind and Sutton 1960) that demonstrated cellular repair processes: Fig.2 is the fractionated survival curves with V79-1 cells after 2.5 and 23 hours of incubation at 37℃ after a first dose of 5.05 Gy and the non-fractionated curve after 2 hours at 37℃ for attachment. It was interpreted in the following way; the first dose of 5.05 Gy killed a number of cells whereas other cells attained damage that it is called "sublethal damage," but in the time interval between the two doses the damage could be repaired and the cells were "heathier" when the next dose hit.

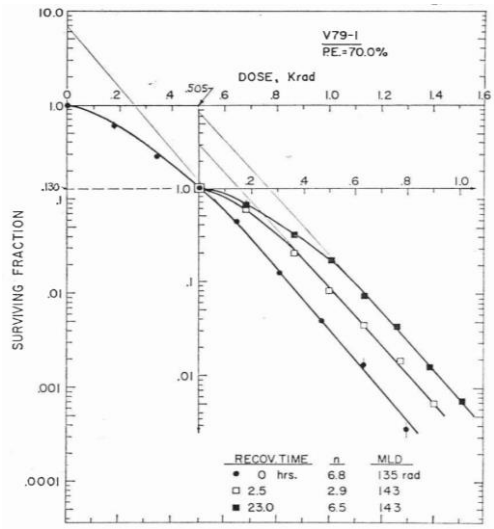
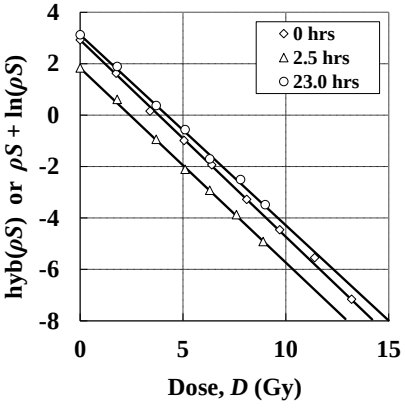
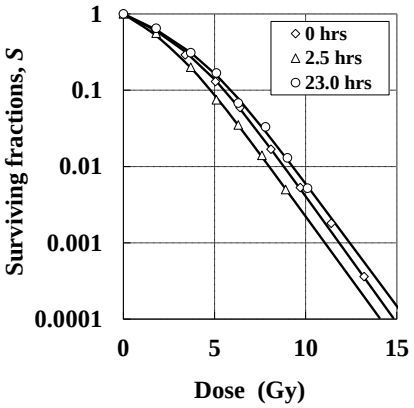


Fig.2 Split-dose mice experiment [6].



(a) Hybrid-Linear plots



(b) Semi-Log plots

the HS model of cell survival with repair as follows:
$\mathbf{hyb}(\boldsymbol{\rho S}) = \boldsymbol{\delta - \lambda D},\ \boldsymbol{\delta} = \mathbf{hyb}(\boldsymbol{S})$

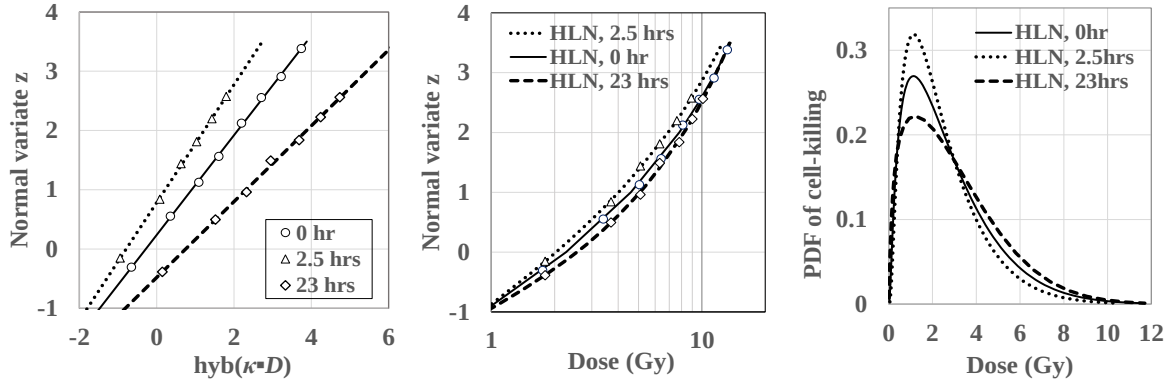
hour	ρ	λ (Gy^{-1})	δ
0.0	2.156	0.765	2.925
2.5	1.456	0.756	1.831
23.0	2.294	0.741	3.124

(c) Estimated parameters

Fig.3 Results of the HS model (bold line) fitted to three sets of data after a first dose shown in Fig.2.

Fig.3 shows results of the HS model fitted to each of data after a first dose of 5.05 Gy in Fig.2. Fig.3 (a) shows the three arrays of data plots (◇, △, ○) lying good on each of three mutually parallel straight lines (solid lines), and the value of ρ is smaller for the lower array of plots (△) due to insufficient repair of 2.5 hours of incubation but it is larger for the higher arrays of plots (◇, ○) due to sufficient repair. Thus it was proved that the hybrid scale model fits well to data of cell survival with the shouldered survival curve and the value of δ = hyb (ρ) at D = 0 indicates the magnitude of the overall effectiveness of cell repair.

The probability of cell killing is $K = 1 - S$. To find the most frequency of occurring the cell death, fitting the HLN model to the same data (Elkind and Sutton 1960), each of the HLN plots is linear for 0.0, 2.5 and 23.0 hours of incubation, respectively, shown in Fig.4 (a). The LN (log-normal) plots in Fig.4 (b) shows that the half of cells are killed below 2 Gy for 2.5 hours, below 2.3 Gy for 0 hour and below 2.5 Gy for 23 hours of incubation. The probability density functions (pdfs) of cell killing have similar modes of dose (but $\text{mode}_{2.5\text{h}} \approx 1.1$ Gy < $\text{mode}_{0\text{ h}}$ < $\text{mode}_{23\text{h}} \approx 1.2$ Gy) but the magnitude of mode is the largest for 2.5 hours and the smallest for 23 hours, while the magnitude of pdf is the smallest for 2.5 hours and the largest for 23 hours. Thus the HLN analysis provides detail profiles of statistical characteristics about cell repair processes.



(a) HLN plots (b) LN plots (c) pdfs of cell killing

Fig.4 HLN Probability density functions of cell killing calculated from data shown in Fig.1.

As mentioned above, first the dose kinetics of cell repair processes can be describe as a simple model with combining the law of proportionate effect and the feedback mechanism, called "the hybrid scale model of cell survival," second the shouldered surviving curves can be transformed into the linear graphs that are mutually parallel under the similar inactivation constant but cell repair processes change the overall effectiveness (i.e., modify the value of ρ) according to incubation time after first dose, and third the hybrid lognormal (HLN) analysis can also be applicable to data of the probability of cell death via cell repair processes. Thus it suggests the hybrid function hyb (ρX) or hyb (ρS) is essential to formulate how it reasonably controls a relevant quantity with a control parameter ρ of feedback mechanism.

DOSE-RESPONSE RELATIONSHIPS

Models of dose-response relationships have been developed depending on the knowledge of biological findings and mathematical analysis developments. The linear-quadratic (LQ) model and the generalized linear-quadratic (GLS) model are the most common in various relevant fields. Preston et al. [7] reported the challenge of developing a biologically based computational model to minimize uncertainty in dose-response

modeling, summarized as understanding a sufficient amount of the relevant biology; acquiring enough data to parameterize the model; and developing the computational model. The development of biologically based dose-response (BBDR) models includes the two-stage clonal growth model and the multistage clonal expansion model to assess the impact of tumor progression on cancer incidence curves.

The LQ or GLQ model can apply to data of cancer incidence as well as chromosome aberrations. According to the preliminary analyses based on combining the law of proportionate effect and the feedback mechanism of excess adverse effect control, the generalized hybrid scale (GHS) model is also applicable to data of chromosome aberrations and cancer incidence due to ionizing radiation [8]:

$$\mathbf{ln}\, \boldsymbol{I}(\boldsymbol{D}) = \mathbf{ln}\, \boldsymbol{F}(\boldsymbol{D}) + \mathbf{ln}\, \boldsymbol{S}(\boldsymbol{D}),\ \mathbf{ln}\, \boldsymbol{F}(\boldsymbol{D}) = \boldsymbol{\alpha} + \boldsymbol{\beta}\mathbf{hyb}\,(\boldsymbol{\tau D}), \text{and}\ \boldsymbol{S}(\boldsymbol{D}) = \mathbf{cyb}\,(\boldsymbol{\delta} - \boldsymbol{\lambda D})/\boldsymbol{\rho},$$

where $I(D)$ is the incidence of adverse effects (minus background) at dose D (Gy), $F(D)$ is the HS model of incidence per viable cell with non-dimensional constants α, β and dose scaling factor τ (Gy^{-1}), and $S(D)$ is the HS model of cell survival with constants λ (Gy^{-1}) and non-dimensional constant δ = hyb (ρ), mentioned above. The inverse function of hyb (x) denotes cyb (x), called "the cyb function."

$F(D)$ is the product of the power model $(D / D_0)^b$ or $a D^b$ and the incidence acceleration term $e^{c D}$, where $F(D) = e^{\alpha} (\tau D)^{\beta} e^{\beta \tau D} = a D^b e^{c D}$. Sax (1940) [9] reported that if each aberration is dependent upon one break or two breaks only, the frequency of aberrations should increase approximately as the linear or the square of dose, respectively, while the frequency of aberrations increases approximately on the 3/2 power of dose varied by varying the time of exposure. For risk assessment the power model is preferable due to occurring various breaks simultaneously. When dose becomes higher, a complex system of repair processes becomes out of work at an accelerated pace with $e^{c D}$. It is a biological interpretation of the HS model of $F(D)$.

In cancer incidence, we should consider the whole story of tumors from initiation to cancer incidence or death, including various modifiers and competitive factors finally. It is a stochastic process of tumor growth so that the probability of occurring tumors should be distributed significantly in some finite range of dose. Putting the incidence per viable cell F divided by its maximum F_{max}, $0 < F / F_{max} < 1$, and $W = \ln [(F / F_{max}) / \{1 - (F / F_{max})\}]$, $-\infty < W < +\infty$, we have the probability of tumor prob $\{D < d\} \approx F / F_{max}$, expressing as a form of $W = \alpha + \beta$ hyb (τD). For $F \ll F_{max}$, $W \approx \ln (F) - \ln (F_{max}) \ \therefore \ln F(D) = \alpha + \beta$ hyb (τD). Analogous to the stochastic process in radiation exposure balancing between dose-increasing force and dose-constraint control, the stochastic process in tumor growth can be assumed to balance between dose-increasing within repairable situations and repair-function decline. Then the dose required for unit ratio of incidence per viable cell $dD / d \ln\{F(D)\} = (D / \beta) / (1 + \tau D)$ becomes $dD / d \ln\{F(D)\} \approx (D / \beta)$ for $\tau D \ll 1$ that is more dose to cause the unit ratio increase of incidence and becomes $dD / d[F(D)] \approx 1 / \beta \tau$ for $\tau D \gg 1$ that is a constant not depending on dose.

Experimental data I - Chromosome aberrations of mice by x rays

To understand the basic characteristics of dose-response relationships, experimental data is rather better than epidemiological data. Preston and Brewen (1973) reported the frequency of reciprocal translocations induced by x-ray irradiation of mouse spermatogonial cells measured over a dose range of 0 – 1200 R (Fig.5). They selected the best fit model $Y = b D + c D^2$ to data for the dose rage 0 - 500 R. The yield of translocations above 600 R decreased by dose, leading to a "hump-shaped" dose-response curve over whole dose range

studied. Authors suggested 0.86 Gy = 100 R for the testes absorbed dose, but we use 1 Gy = 100 R without no generality for the following analysis.

The "hump-shaped" curve $Y(D)$ can be given by the product of the yield per viable cell $F(D)$ and the cell survival $S(D)$, that is $Y(D) = F(D) \times S(D)$. The HS models are $S(D) = \text{cyb}(\delta - \lambda D) / \rho$ and $\ln[F(D)] = \alpha + \beta\, \text{hyb}(\tau D)$, then the generalized hybrid scale (GHS) model is $\boldsymbol{Y(D) = a\, D^b \exp(c\, D) \times \text{cyb}(\delta - \lambda D) / \rho}$ or $\boldsymbol{\ln[Y(D)] = \alpha + \beta\, \text{hyb}(\tau D) + \ln[\text{cyb}(\delta - \lambda D) / \rho]}$ for data in Fig.5.

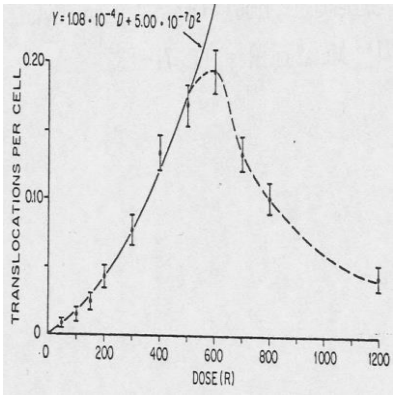


Fig.5 Data of Translocations. (Preston and Brewen, 1973)[10]

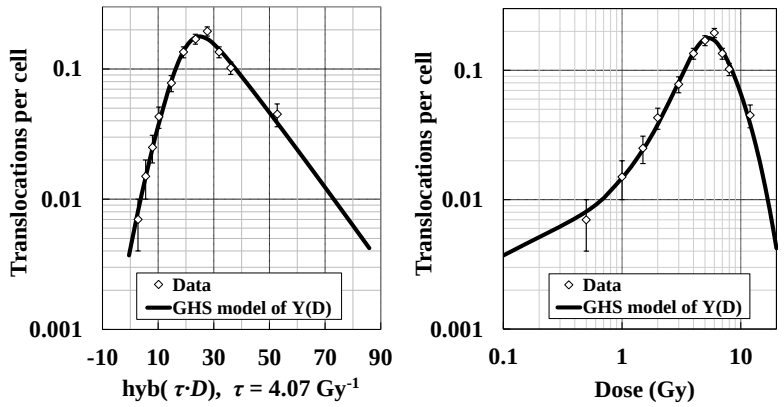
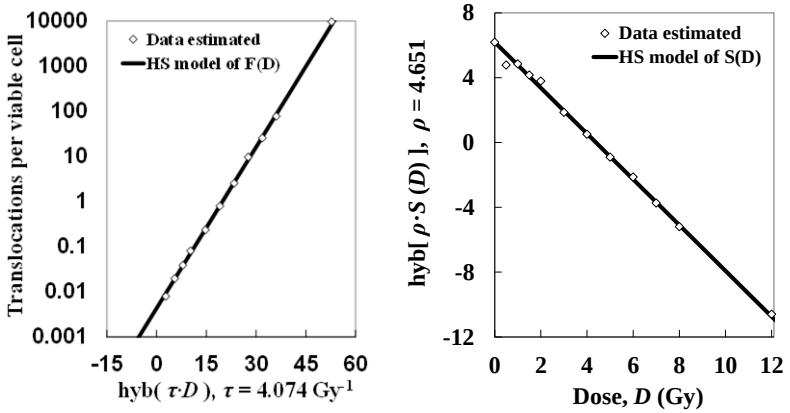


Fig.6 The GHS model of $Y(D)$ fitted to data in Fig.5. Left: log-hybrid plots of data, right: log-log plots of data.

Fig.6 demonstrates a good fit of the GHS model $Y(D)$ (bold line) to translocations per cell (◇) over the dose range of 50 -1200 R in Fig.5, where the estimated GHS model is $\ln(Y) = -5.05 + 0.27\, \text{hyb}(4.07\, D) + \ln[S(D)]$ and $\text{hyb}[4.65\, S(D)] = 6.19 - 1.41\, D$. The estimated HS models of $F(D)$ and $S(D)$ are linear on log-hybrid plots and on hybrid-linear plots, respectively. Data estimated (◇) in Fig.7 (a), (b) are the calculated translocations per viable cell, that is data in Fig.5 divided by $S(D)$ and the calculated survivals, that is data in Fig.5 divided by $F(D)$, respectively. Thus the HS models of $F(D)$ and $S(D)$ demonstrates a good fit.

hybrid plots and on hybrid-linear plots, respectively. Data estimated (◇) in Fig.7 (a), (b) are the calculated translocations per viable cell, that is data in Fig.5 divided by $S(D)$ and the calculated survivals, that is data in Fig.5 divided by $F(D)$, respectively. Thus the HS models of $F(D)$ and $S(D)$ demonstrates a good fit.



(a) Log-hybrid plots (b) Hybrid-log plots

Fig.7 The HS models $F(D)$ and $S(D)$ fitted to data shown in Fig.5.

Experimental data II – Myeloid leukemia of mice by x rays

Next we examine how the hybrid scale model fits the incidence of myeloid leukemia of mice by x rays. The UNSCEAR 1986 Report [11] discussed about such data from Mole (1984) and Di Majo (1986) as shown in Fig.7 and selected the best-fit model, $I = a_2\, D^2 \exp(-\beta_1\, D)$, of dose-response by fitting a four-term

polynomial of the general form $I = (a_1 D + a_2 D^2) \exp(-\beta_1 D - \beta_2 D^2)$. Here estimating the parameters of the same model excluding data at 6 Gy because of the negative value of the incidence, we obtain $I = 20.35D^2 e^{-0.81D}$ with AIC = -4.595 or SSE = 7.577 where AIC is Akaike Information Criteria and SSE is the sum of squared errors. This result shows in Fig.8 (a), considerably similar to that in Fig.7.

To apply the GHS model to data in Fig.7 we had $I(D) = 1.61D^{2.44} e^{17.47D}$ cyb(2.63 – 18.45D) / 1.96 with AIC= -5.843 or SSE= 3.843. According to the estimates of AIC, the GHS model is better that the model of $I = a_2 D^2 \exp(-\beta_1 D)$. Thus the GHS model is applicable to data in Fig.7 while cell survivals estimated by the HS model decrease too steep by dose (inactivation constant $\lambda = 18.45$ Gy^{-1}).

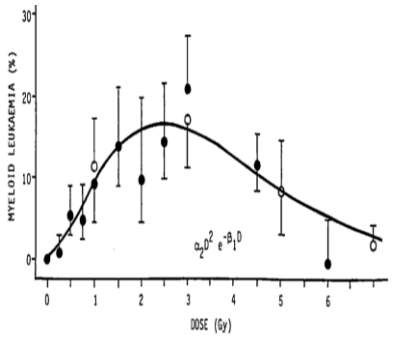
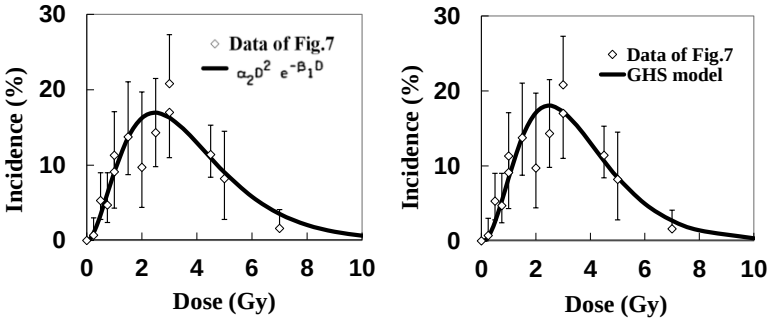


Fig.7 Data of Myeloid leukemia (Mole,'84; Di Majo et al., '86) [11]



(a) $I=a_2D^2\exp(-\beta_1 D)$, AIC -4.595 (b) The GHS model, AIC -5.843

Fig.8 Dose-response models fitted to data shown in Fig.7.

Epidemiological data – LSS solid cancer incidence 1958-1998

The model of dose-response relationships should be applicable to human exposure data for risk assessment. The GHS model have been applied to the mortality and incidence of solid cancers and leukemia among A-bomb survivors since late 1980s by authors. Fig.9 shows the solid cancer incidence dose-response in A-bomb survivors for years 1958 - 1998 (Preston et al., 2007) [12]. Including the cell sterilization (killing) effect, the GHS model was fitted well to data (◇) of excess relative risk (ERR) of solid cancer incidence from Fig.9.

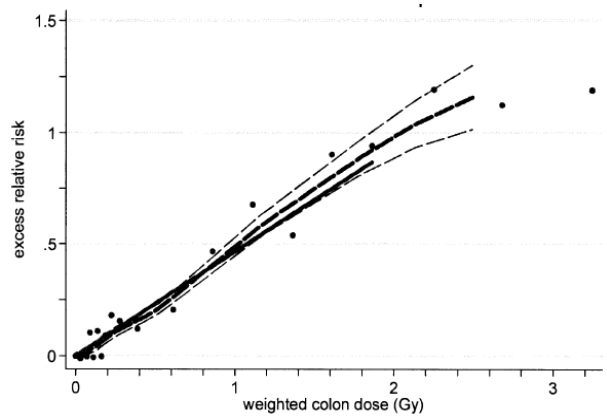


FIG. 3. Solid cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a nonparametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth.

Fig.9 LSS solid cancer incidence (1958-1998)

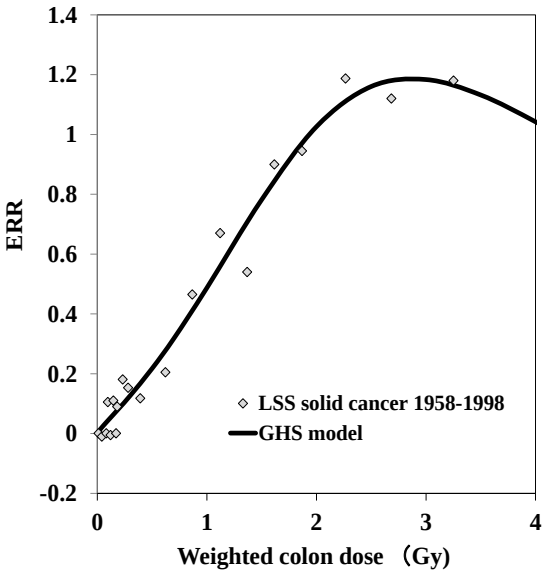


Fig.10 The GHS model fit to data from Fig.9

In Fig.11 two arrays of data (◇) of ERR (Fig.9) divided by S(D) and F(D) estimated by the GHS model are approximately straight on log-hybrid plots and on hybrid-linear plots, respectively, where two negative ERR data are not plotted because of logarithmic and hybrid functions defined for positive value. There are significant variations in the lower dose range but the whole plots of each array of data can be explained by the HS models considerably. Thus the HS models and GHS model demonstrate a good fit to the LSS data.

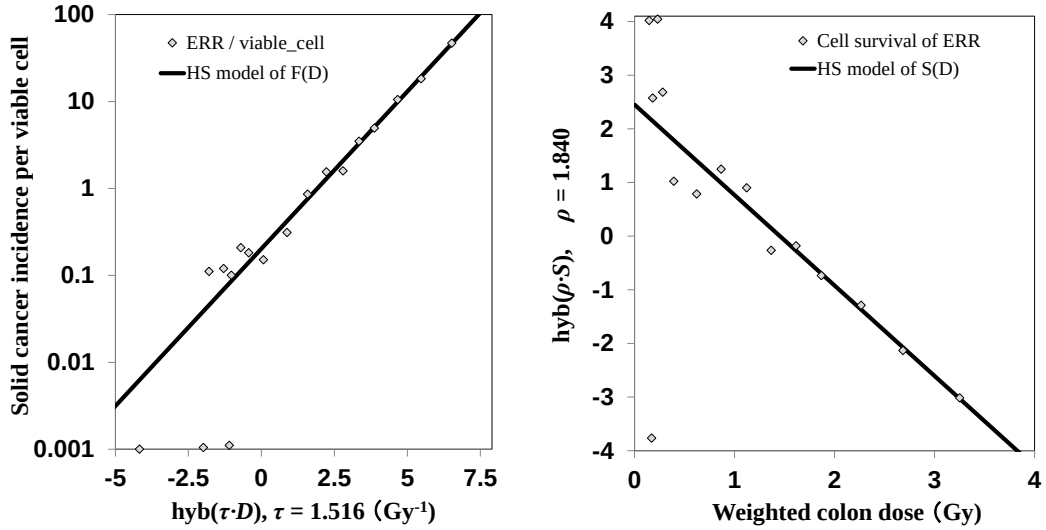


Fig.11 HS models fit to data of ERR in Fig.9. Left: ERR per viable cell, right: cell survival.

DISCUSSION

Starting from the dose distribution analysis relating to the quantitative formulation on reasonable risk control, the paper described the characteristics of the hybrid function and its applicability to dose-response relationships, including the shouldered survival curve and the "hump-shaped" dose-response curve (or that with cell sterilization effect). For the low-dose risk assessment we need not to consider the cell sterilization effect. However, to understand the strategy of bio-systems coping with adverse effects as a whole, we should find the basic mathematical feature of risk control function that should obey the law of efficient consumption of available energy and resource.

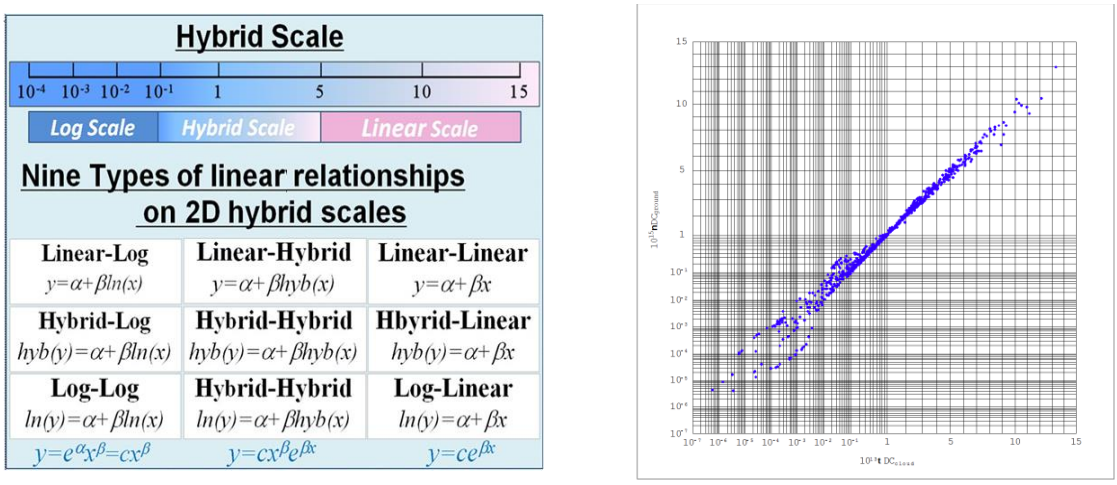


Fig.12 A summary of the hybrid scale and its 2-dimensional application as "the hybrid-hybrid section paper."

The hybrid scale shown in Fig.12 is similar to the logarithmic scale at less than 0.1 as well as the linear scale at more than 5. The range between 0.1 and 5 is neither the logarithmic nor the linear but truly their hybrid scale. The hybrid scale is a scale of x corresponding to the linear scale of y via the hybrid function y = hyb(x). In an exposure process we do not care so much about insignificant dose but care the more about the larger dose increment on an average. This stochastic process of exposure consists of three situations: insignificant risk, tolerable risk and intolerable risk.

As for dose distribution analysis, it was proved that the stochastic process of dose accumulation generates the HLN distribution of individual doses at the end of a time interval (0, T) based on the Martingale central limiting theorem. The HLN distribution provides the maximum entropy of occurring individual doses among a homogeneous populations (however mixing various types of lognormal and normal variations) as the normal distribution via the hybrid function of dose. Experimentally acquired values of parameter ρ bring the variation of worker doses in the range of 0.1 to 5 of dose multiplied by ρ, where ρ is very small at low dose-rate work environment. At higher dose rate workplace there finds the HLN of y = (dose – a) / (b – dose) where a < dose < b, where the characteristics of the hybrid function is also important in the range of 0.1 to 5.

This paper raises a question whether the function of bio-systems against adverse effects shows the characteristics of the hybrid function corresponding to three risk regions: insignificant, tolerable and intolerable risks. Data of Elkind and Sutton (1963) demonstrated the dose kinetics of cell repair processes and their concept "sublethal damage" possible to repair damages with sufficient incubation time depending on dose and dose rate. This phenomena can be well modeled by the hybrid scale (HS) model installed the feedback mechanism with parameter ρ to repair sublethal cells depending on $S(D)$. The magnitude of ρ can explain the different effectiveness of incubation time after a first dose corresponding to their explanation.

Data of Preston and Brewen (1973) provided the "hump-shaped" dose-response curves of translocations of mice over the whole dose range, discussing about dose rate effects and resistant / sensitive cell populations or a heterogeneously mixed population producing after irradiation of moderate to higher doses. Their dose-response data was successfully fitted by the generalized hybrid scale (GHS) model. Thus the characteristics of the hybrid function is effective to explain the frequencies of translocations per viable cell with the increase of dose as well as cell survival with the repair effects of sublethal damage depending on the degree of healthy cell via S(D). The GHS model also fitted data of Mole (1984) and Di Majo et al. (1986) for incidence of myeloid leukemia after brief exposure of male CBA mice over the whole dose range, cited from the Annex B of the UNSCEAR 1986 Report. According to AIC, the GHS model is slightly better than the best fit model reported by the UNSCEAR. Thus the GHS model is applicable to dose-response relationship of data including the tumor process as well as that of data of chromosomal aberrations.

The GHS model has been fitted to data of LSS since late 1980s. The LSS solid cancer incidence 1958-1998 was fitted by the GHS model nicely. Thus the GHS model is applicable to dose-response relationship of LSS cancer data. The LSS solid cancer mortality 1950-2003 (Ozasa et al. 2013) can also be fitted by the HS model good but it demonstrates no cell sterilization effect due to data below 3 Gy that makes a difficulty to fit the GHS model to data. However they reported the graph of *ERR* per *Gy* for all solid cancer for selected dose ranges the result of which shows that the increased *ERR*/*Gy* in the low-dose levels less than 0.1 Gy

corresponds to the estimates of ERR higher than the expected linear dose-response determined from data in the whole range of dose.

The GHS model results in the increased d*I*/dD with decreasing dose in the low-dose range for LSS solid cancer mortality 1950-2003 as well as most of other LSS data of mortality and incidence. The increased d*Y*/d*D* or d*I*/d*D* with decreasing dose in the low-dose range less than 0.1 Gy demonstrated by fitting the GHS model to data of Preston and Brewen (1973) and data of Mole (1984) and Di Majo et al. (1986). The age-specific mortality rate of Japanese male 2000 also shows the increased mortality rate with becoming younger ages less than about 14 years old. The age specific mortality of experimental mice also demonstrates similar characteristics. Ages seems to represent an amount of accumulating toxic exposure in life. Thus d*I*/d*D* or d*Mortality*/d*Ag*e demonstrates basically V-shape on log-hybrid plots of (*D*, *I*) or (age, mortality rate). This subject is important to understand the risk control strategy over lifetime.

CONCLUSION

This paper presented the definition, meaning, application of the hybrid function in terms of reasonable risk control from radiation protection to biological protection against adverse effects. It was proved that the hybrid scale defined via the hybrid function affords a linearized relationship between two quantities after appropriately decomposing the original quantities, e.g. decomposing $I(D)$ into $F(D)$ and $S(D)$. The paper showed the importance of the range 0.1 to 5 on the hybrid scale for achieving the reasonable risk control.

REFERENCES

(1) ICRP. Recommendations of ICRP, ICRP Pub.26, Annals of the ICRP 1(3) Pergamon Press, Oxford, 1977.
(2) UNSCEAR. Ionizing radiation sources and biological effects, Annex H, UNSCEAR 1982 Report to the General Assembly, Annex H, United Nations, New York, 1986.
(3) Kumazawa, S. and Numakunai, T. A new theoretical analysis of occupational dose distributions indicating the effect of dose limits. Health Phys. 41(3), 465-475, 1981.
(4) Kumazawa, S. and Numakunai, T. Why do we need dose distribution model? Radiat. Prot. Dosim. 36 (2/4), 269-273, 1991.
(5) Henriksen, T. and Biophysics group at UiO. Chapter 12. Cellular radiation damage and repair, Radiation and Health, https://www.mn.uio.no/fysikk/tjenester/kunnskap/straling/radiation-and-health-2013.pdf.
(6) Elkind, M.M. and Sutton, H. Radiation response of mammalian cells grown in culture, I. Repair of x-ray damage in surviving Chinese hamster cells. Radiat. Res. 13, 556-593, 1960.
(7) Preston, R.J., et al. Uncertainties in estimating health risks associated with exposure to ionising radiation. J. Radiat. Prot. 33, 573-588, 2013.
(8) Kumazawa, S. Biological risk control model based on the law of randomly proportional effect with feedback. 2011 KAKENHI Symposium on life science and statistics, Sigma Hall of Osaka Univ., 2011.11.3 - 5. (In Japanese)
(9) Sax, K. An analysis of x-ray induced chromosomal aberrations in Tradescantia. Genetics 25, 41-68, 1940.
(10) Preston, R.J. and Brewen, J.G. X-ray-induced translocations in spermatogonia: I. Dose and fractionation responses in mice. Radiat. Res. 19, 215-223, 1973.
(11) UNSCEAR. Genetic and somatic effects of ionizing radiation, Annex B, UNCEAR 1986 Report to the General Assembly, United Nations, New York, 1986.
(12) Preston, D.L., et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat. Res. 168, 1-64, 2007.
(13) Ozasa, K., et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overall of cancer and noncancer diseases. Radiat. Res. 177, 229-243, 2012.