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IMPROVED CONFIDENCE LIMITS FOR LOW-DOSE CARCINOGENIC RISK ASSESSMENT FROM ANIMAL DATA*

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Summary

An improved procedure is presented for estimating low-dose risks from dichotomous animal data. Based on the multistage model of cancer, the procedure gives a maximum likelihood fit to the experimental data. Because the model is approximately linear in the low-dose range, the procedure may be considered to be a generalized method for linear extrapolation which uses all of the data. The extrapolation procedure is different from an earlier procedure based upon the multistage model in that two improved methods are put forward for calculating statistical confidence limits. (One is a linearized approximation of the other.) A further innovation is a recommendation for the integration of several data sets in the calculation of risk levels.

Introduction

Toxicological carcinogenicity experiments frequently have as a primary goal the determination of whether a chemical will induce tumors under given experimental conditions. However, since it is becoming increasingly clear that all carcinogens cannot be banned, it is also important to have a quantitative measure of the carcinogenic potency of a chemical. This measure of potency should be related to doses near to those experienced by humans. Such doses are generally much lower than those used in an experimental setting.

One general procedure for estimating potency involves the fitting of a mathematical dose—response model to experimental data and predicting low-dose risks from the fitted model. Such procedures are increasingly being applied to experimental carcinogenicity data, and the outputs from these procedures are beginning to be used in the regulatory process [1, 2]. Since both the human health and economic consequences of regulatory decisions can be enormous, it is important to apply the most scientifically valid risk assessment procedures available.

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The purpose of this paper is to improve and extend the extrapolation procedure proposed by Crump et al. [3] based upon a generalization of the Armitage–Doll [4] multistage model of cancer. The multistage model is premised upon plausible, although fairly general, assumptions regarding the initiation and expression of a tumor. The resulting mathematical dose–response function is capable of describing adequately a broad spectrum of data.

Upper statistical confidence limits on risk calculated with the Crump et al. [3] procedure vary linearly with dose in the low-dose range (the low-dose-linearity property). There are some fairly general arguments which suggest that, in many instances, the true dose–response curve should be approximately linear at low doses. These arguments apply particularly to situations in which cancer is initiated through a chain of genetic or epigenetic events which may already be operative and producing background tumors in the absence of the particular chemical under test [3, 5]. A great deal of mutagenicity dose–response data appear to be linear [6], which adds experimental support to the low-dose linear hypothesis. On the other hand, there is neither a convincing model of carcinogenicity nor a body of experimental evidence which suggests a more extreme dose–response behavior at low doses than low-dose linearity. Consequently, low-dose linearity may be the true state of nature in many cases, and when low-dose linearity does not hold, an extrapolation based upon this property should most likely overestimate, rather than underestimate, the true risks.

Hoel et al. [7] proposed, for use on an interim basis, an extrapolation method based upon a simple linear interpolation between the response in the control group and the response in a single treated group. This method, although linear at low-dose, has the drawback of being somewhat ad hoc and not utilizing all the pertinent data.

The one-hit model

$$P(d) = 1 - \exp[-(q_0 + q_1 d)] \tag{1}$$

where $P(d)$ represents the lifetime probability of cancer when subjected to a continuous dose rate d, is the particular case of the multistage model in which there is only one stage. At low doses, the extra risk over background is given approximately by $q_1 d$ and thus is linear at low dose. This model has been proposed for use by the EPA in the setting of water quality criteria [1]. The model has only two parameters and must always exhibit downward curvature everywhere. Whenever it is fit to data that exhibit upward curvature (which is a frequent occurrence), the model may not fit well and is likely to lead to overestimation of risk in the low-dose region. To illustrate this phenomenon, in Fig.1 we have fit both the one-hit model and the multistage model to data of Graham et al. [8] on ethylenethiourea (ETU). The ETU data are given in Table 1. As Fig. 1 illustrates, the one-hit model appears to overestimate the risk in the low-dose range.

Other models which have been proposed for low-dose extrapolation in-

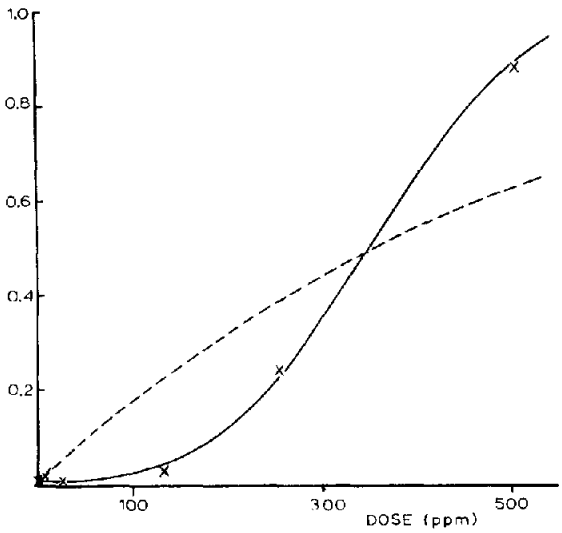

Fig.1. Illustration of the fit of the one-hit model, eqn. (1), and multistage model, eqn. (2), to data in Table 1. ×, Data point; ——— , multistage fit to data; — — —, one-hit fit to data.

TABLE 1

Incidence of thyroid carcinomas in rats exposed to ETU [8]

Dietary concentration (ppm)	Number of animals	Number of tumor-bearing animals	Expected number of tumor-bearing animals	
			One-hit	Multistage
0	72	2	1	1
5	75	2	2	2
25	73	1	4	2
125	73	2	16	3
250	69	16	26	15
500	70	62	43	62

Maximum likelihood estimates of model parameters

One-hit model	Multistage model
$\hat{q}_0 = 0.01209$	$\hat{q}_0 = 0.02077$
$\hat{q}_1 = 0.001852$	$\hat{q}_1 = 0.0$
	$\hat{q}_2 = 0.0$
	$\hat{q}_3 = 1.101 \times 10^{-5}$
	$\hat{q}_4 = 1.276 \times 10^{-11}$
	$\hat{q}_5 = 0.0$

clude the probit model (Mantel et al., [9]) and the multi-hit model [10]. Neither of these models has the low-dose-linearity property.

The multistage model has the form

$$P(d) = 1-\exp[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_K d^K)] \quad (2)$$

where $q_i \geqslant 0$, $i = 0, 1, \ldots, K$. This model contains the one-hit model as a special case and thus will always fit data at least as well as, and frequently much better than, the one-hit model. To illustrate, we note from Fig.1 that the multistage model provides a much more satisfactory fit to the ETU data than the one-hit model. Thus, use of the multistage model can provide better descriptions of the data than the one-hit model, while retaining the low-dose-linearity property of the confidence bounds.

The linearized procedure presented in this paper is based upon a linear approximation to the likelihood ratio confidence bounds which is valid for low doses. This method improves upon the method recommended in Crump et al. [3] in that it is conceptually simpler and is not strongly dependent upon the choice for the parameter K in the multistage model. The likelihood ratio procedure presented here does not require the linear approximation and will therefore provide valid confidence limits over a greater range of doses. The cost of this increased fidelity is more extensive use of nonlinear optimization techniques. In practice, the two methods will be indistinguishable at low doses and in virtual agreement at higher doses (see Table 5). In particular, confidence limits from the likelihood ratio procedure are also linear at low doses.

Another improvement over previous methods is a suggested extrapolation procedure using two or more data sets simultaneously. This procedure permits a balanced approach to extrapolation whenever two or more data sets are available from experiments with equally acceptable protocols.

Methods

The experimental setting is one in which young animals are randomly divided into g treatment groups, the ith group containing N_i animals. Animals in the ith treatment group are administered the chemical at a constant dose rate, d_i, until death. Let x_i represent the number of the total of N_i animals in the ith group which are determined to be tumor-bearing at death. Let $P(d)$ represent the lifetime probability of cancer for the multistage model of cancer given by eqn. (2). By extra risk over background at a dose rate d, we mean the quantity

$$R(d) = [P(d) - P(0)]/[1 - P(0)]$$

which represents the increase in the probability of acquiring a tumor when subjected to a dose rate d, divided by the probability of remaining tumor-free in the absence of the chemical. The extra risk $R(d)$ may also be interpreted as the probability of acquiring a tumor when subjected to a dose

response d, given that no tumor would have been forthcoming in the absence of the chemical insult. It is easily shown that, for the multistage model

$$R(d) = 1-\exp\left[-(q_1 d + q_2 d^2 + \ldots + q_K d^K)\right]$$

and at low doses, we have approximately

$$R(d) \simeq q_1 d \tag{3}$$

In some applications, the additional risk, $AR(d) = P(d) - P(0)$, is of interest. Although we treat only the extra risk in this paper, MLEs and confidence regions for the additional risk may be obtained through the obvious modifications of the methods presented here.

We will develop the linearized extrapolation method from relation (3). It can be seen from this approximate expression that an upper statistical confidence bound for the extra risk at a low dose can be calculated simply by multiplying an upper confidence limit for the linear parameter q_1 by the dose. Similarly, a lower confidence limit for the dose d_R corresponding to a given extra risk R may be obtained by dividing R by the upper confidence limit for the parameter q_1.

The calculation of an upper confidence limit for q_1 will be based upon the log-likelihood of the data. In this experimental setting, the log-likelihood differs by a constant not dependent upon the parameter vector, $\vec{q} = (q_0, \ldots, q_K)$, from (Ref. [3])

$$L(\vec{q}) = \sum_{j=1}^{g} \{X_j \ln P(d_j) + (N_j - X_j) \ln[1 - P(d_j)]\} \tag{4}$$

Let $\hat{\vec{q}}$ $(\hat{q}_0, \ldots, \hat{q}_K)$ denote the (nonnegative) maximum likelihood estimate for $\vec{q}$ obtained by maximizing the log-likelihood $L(\vec{q})$. Now let the linear parameter be increased from $\hat{q}_1$ to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value for the linear parameter, the resulting maximal value $L(\vec{q}^*)$ satisfies the equation

$$2[L(\hat{\vec{q}}) - L(\vec{q}^*)] = 2.70554$$

where 2.70554 is the cumulative 90th percentage point of the chi-square distribution with one degree of freedom. Using the asymptotic distribution of the likelihood ratio [11], it can be shown that the value q_1^* so computed represents, under suitable regularity conditions, an asymptotic upper 95% confidence bound for q_1. (This approach was also used by Mantel et al. [9]). Other confidence bounds for q_1 are computed in the same way using the appropriate point of the chi-square distribution with one degree of freedom.

It follows from eqn. (3) that $q_1^* d$ represents an approximate upper 95% confidence bound on the extra risk $R(d)$ for a given low dose d. Likewise, if the "virtually safe dose" is defined as a lower 95% confidence limit on the dose for which the extra risk $R(d)$ is, say, 10^{-5} then $10^{-5}/q_1^*$ represents a virtually safe dose.

The likelihood ratio extrapolation method is also based upon the approximate chi-square distribution of the log-likelihood function in eqn. (4). The 95% upper confidence limit on extra risk at a dose d is the largest extra risk R' which satisfies

$$\frac{P(d;\vec{q}') - P(0;\vec{q}')}{1 - P(0;\vec{q}')} = R' \tag{5}$$

(i.e., R' is the extra risk at dose d based upon the parameter vector $\vec{q}'$) and

$$2[L(\hat{\vec{q}}) - L(\vec{q}')] = 2.70554 \tag{6}$$

for some coefficient vector $\vec{q}' = (q_0', \ldots, q_K')$ where, as before, $\hat{\vec{q}}$ is the maximum likelihood estimate of the coefficient vector $\vec{q}$ and 2.70554 is the 90th percentage point of the chi-square distribution with 1 degree of freedom. Similarly, the 95% lower limit on the dose d corresponding to an extra risk of R is the smallest dose d' which satisfies

$$\frac{P(d';\vec{q}') - P(0;\vec{q}')}{1 - P(0;\vec{q}')} = R \tag{7}$$

i.e., d' is the safe dose corresponding to an extra risk of R, based upon the vector $\vec{q}'$ which satisfies eqn. (6). Confidence limits using additional risk are defined analogously by replacing the expressions for extra risk in eqns. (5) and (7) by the corresponding expressions for additional risk. Confidence limits of other sizes are obtained by replacing 2.70554 by the appropriate percentage point of the chi-square distribution with 1 degree of freedom.

If there are $s > 1$ data sets available for extrapolation to low dose, a similar approach can be used. Suppose the rth data set contains the experimental doses $D_{1r}, \ldots, D_{g_r r}$ with corresponding numbers of animals $N_{1r}, \ldots, N_{g_r r}$ and numbers of tumor-bearing animals $X_{1r}, \ldots, X_{g_r r}$. To combine the data sets, it will be assumed that there is a spontaneous background parameter q_{0r} peculiar to the rth data set but the remaining parameters $q_1, \ldots, q_K$ are common to all s data sets. Thus for the rth data set, the response probability is of the form

$$P_r(d) = 1 - \exp[-(q_{0r} + q_1 d + q_2 d^2 + \ldots + q_K d^K)]$$

The log-likelihood of the combined s data sets differs by only a constant from

$$L = \sum_{r=1}^{s} \sum_{j=1}^{q_r} \{ X_{jr} \ln P_r(d_{jr}) + (N_{jr} - X_{jr}) \ln [1 - P_r(d_{jr})] \}$$

The statistical procedures described above for a single set of data are applied without change to this log-likelihood to calculate statistical confidence bounds.

Throughout this discussion, we have assumed that the parameter K in the model (2) is known. This does not represent an untenable restriction

because, as noted below, the value of K is not critical in practice. Since some of the parameters q_i may be zero, K represents only an upper bound to the allowable number of stages in the multistage model, rather than the actual number of stages. To permit the greatest flexibility for the model, it seems desirable to make K fairly large subject to the obvious constraint that there should be no more parameters in the model than there are dose groups. (Even this constraint is not absolutely necessary.) On the other hand, computational difficulties arise if K is excessively large. Thus, we recommend choosing $K = \min(6, g-1)$. This choice makes the number of possible parameters equal to the number of dose groups whenever the number of dose groups is no larger than 7. In practice, this choice is not at all critical. Generally, a K value of around 3 will yield very nearly the same confidence limits as larger values of K. In this regard, the methods proposed here are superior to the method proposed by Crump et al. [3]. The choice of K was a critical decision in the earlier approach. It should also be kept in in mind that in choosing K one is not selecting the number of stages, but only setting an upper bound on the permissible number of stages allowed in fitting the model.

As a heuristic measure of the goodness of fit of the multistage model, Crump and Watson [12] suggest the chi-square statistic

$$\sum_{i=1}^{g} \frac{[X_i - N_i P(d_i)]^2}{N_i P(d_i)\,[1-P(d_i)]}$$

Assessing the statistic is difficult due to the non-standard situation resulting from the nonnegativity constraints on the multistage coefficients $q_1, \ldots, q_K$. Crump and Watson suggest comparing the statistic with the critical value of the chi-square distribution with degrees of freedom equal to g–(number of q_is whose MLEs are positive). For example, if $g = 5$, $K = 4$, and only q_0 and q_1 are positive, the degrees of freedom would be taken to be 3. This approach would lead to a theoretically valid goodness-of-fit test if it were known a priori that the q_i values with zero MLEs were truly zero and that all other q_i values were truly positive.

Examples and discussion

To illustrate the properties of the extrapolation methods as recommended for a single data set, we have applied them to the data for ETU in Table 1 and to the data for hexachlorobenzene (HCB) in Table 2. The two data sets are representative of two distinct situations; the HCB data exhibit downward curvature and are described well by both the one-hit and multistage models, whereas the ETU data exhibit strong upward curvature and are described very adequately by the multistage model, but very poorly by the one-hit model (see Fig.1). Maximum likelihood estimates of additional risk and upper 95% confidence limits thereon are presented in Table 3 for HCB

TABLE 2

Tumor incidence in male hamsters exposed to HCB in the diet [13]

Dietary concentration (ppm)	Number of animals	Number of tumor-bearing animals	Expected number of tumor-bearing animals	
			One-hit	Multistage
0	40	3	3	3
50	30	18	20	19
100	30	27	26	26
200	57	56	56	56

Maximum likelihood estimates of model parameters

One-hit model	Multistage model
$\hat{q}_0 = 0.07552$	$\hat{q}_0 = 0.07678$
$\hat{q}_1 = 0.01975$	$\hat{q}_1 = 0.01773$
	$\hat{q}_2 = 1.589 \times 10^{-5}$
	$\hat{q}_3 = 0.0$

TABLE 3

Estimates of low-dose risk from HCB male hamsters derived from the one-hit and multistage models

Dose level (ppm)	Maximum likelihood estimates of extra risk		95% Upper confidence limits on extra risk	
	Multistage model	One-hit model	Multistage model	One-hit model
10^{-2}	1.8×10^{-4}	2.0×10^{-4}	2.5×10^{-4}	2.5×10^{-4}
10^{-3}	1.8×10^{-5}	2.0×10^{-5}	2.5×10^{-5}	2.5×10^{-5}
10^{-4}	1.8×10^{-6}	2.0×10^{-6}	2.5×10^{-6}	2.5×10^{-6}
10^{-5}	1.8×10^{-7}	2.0×10^{-7}	2.5×10^{-7}	2.5×10^{-7}

using both the one-hit and multistage models. (For all doses considered in Table 3, the multistage model confidence limits based upon the linearized and the exact extrapolation methods were in agreement up to at least three significant digits.) The methodology for the one-hit model was exactly as described earlier in the paper for the multistage model except for setting $K = 1$. The maximum likelihood estimates of risk are very close together for the two models and the upper confidence bounds are indistinguishable. This illustrates some very important properties of the multistage extrapolation procedures.

Multistage extrapolation will never yield low dose risk estimates which are larger than those resulting from one-hit extrapolation. Further, whenever the data can be adequately described by the one-hit model, the two procedures will yield comparable results. This is true regardless of the upper bound K selected for the number of stages.

The comparable behavior of the multistage and one-hit procedures when applied to the ETU data is given in Table 4. Here, the multistage maximum likelihood estimates of risk are far smaller than the one-hit estimates. This is primarily because the maximum likelihood estimate of the linear and quadratic terms q_1 and q_2 were zero, which implies that the multistage maximum likelihood risk estimates vary as the cube of dose. However, the multistage upper confidence bounds vary linearly with dose. The resonableness of such behavior has been discussed in some detail earlier by Guess et al. [14]. Small data shifts, which could occur with appreciable probability, would change the estimated linear term from exactly zero to a positive value, thereby forcing the multistage maximum likelihood estimates of risk to vary linearly with dose instead of as the cube of dose. Thus, it is reasonable that in the low dose range the multistage confidence bounds vary linearly with dose even when the maximum likelihood estimates vary as the cube of dose.

TABLE 4

Estimates of low-dose risk from ETU derived from the one-hit and multistage models

Dose level (ppm)	Maximum likelihood estimation of extra risk		95% Upper confidence limits on extra risk	
	Multistage model	One-hit model	Multistage model	One-hit model
10^{-1}	1.1×10^{-11}	1.9×10^{-4}	3.7×10^{-5}	2.2×10^{-4}
10^{-2}	1.1×10^{-14}	1.9×10^{-5}	3.7×10^{-6}	2.2×10^{-5}
10^{-3}	1.1×10^{-17}	1.9×10^{-6}	3.7×10^{-7}	2.2×10^{-6}
10^{-4}	1.1×10^{-21}	1.9×10^{-7}	3.7×10^{-8}	2.2×10^{-7}

In fact, a more precise examination of the confidence limits based upon linearized and exact methods (Table 5) reveals that, not only do the multistage confidence bounds vary linearly at low doses, but the linearized and exact extrapolations agree to three significant digits for doses as large as 50 ppm.

The multistage confidence bounds on extra risk are smaller than the corresponding one-hit bounds by a factor of about six (Table 4). We have already noted from an inspection of Fig. 1 that the one-hit model seems likely to overestimate the risk.

TABLE 5

Upper confidence limits on extra risk due to ETU derived from linearized and likelihood ratio extrapolation of multistage model

Dose level (ppm)	Maximum likelihood estimates of extra risk	95% Upper confidence limits on extra risk	
		Linearized extrapolation	Likelihood ratio extrapolation
100	1.2×10^{-2}	3.71123×10^{-2}	4.02546×10^{-2}
50	1.5×10^{-3}	1.85561×10^{-2}	1.85833×10^{-2}
10	1.1×10^{-5}	3.71123×10^{-3}	3.70467×10^{-3}
1	1.1×10^{-8}	3.71123×10^{-4}	3.71054×10^{-4}
0.1	1.1×10^{-11}	3.71123×10^{-5}	3.71116×10^{-5}
0.01	1.1×10^{-14}	3.71123×10^{-6}	3.71122×10^{-6}

In Table 6 are exhibited virtually safe doses corresponding to 95% levels of confidence calculated for the ETU data and the HCB male mice data. We note that virtually safe doses vary linearly with extra risk for both the one-hit and multistage models.

The ETU data illustrate the advantage which the use of the multistage model has over the one-hit model in the setting of confidence limits: The multistage methodology yields more reasonable estimates of risk by providing better descriptions of experimental data, while at the same time retaining the low-dose linear property of the confidence bounds.

TABLE 6

Virtually safe doses corresponding to 95% levels of confidence from two data sets

HCB male hamster data (Table 1)			ETU data (Table 2)	
Extra risk	One-hit	Multistage	One-hit	Multistage
10^{-4}	4.0×10^{-3}	4.1×10^{-3}	4.5×10^{-2}	2.7×10^{-1}
10^{-5}	4.0×10^{-4}	4.1×10^{-4}	4.5×10^{-3}	2.7×10^{-2}
10^{-6}	4.0×10^{-5}	4.1×10^{-5}	4.5×10^{-4}	2.7×10^{-3}
10^{-7}	4.0×10^{-6}	4.1×10^{-6}	4.5×10^{-5}	2.7×10^{-4}

To illustrate the application of the procedure to multiple data sets, we have applied it to the combined data consisting of the males and females exposed to HCB. The data for females are in Table 7 and virtually safe doses calculated from the combined data as well as for males and females con-

TABLE 7

Tumor incidence in female hamsters exposed to HCB in the diet [13]

Dietary concentration (ppm)	Number of animals	Number of tumor-bearing animals	Expected number of tumor-bearing animals	
			One-hit	Multistage
0	39	5	5	5
50	30	16	14	14
100	30	18	20	20
200	60	52	52	52

Maximum likelihood estimates of model parameters

One-hit model	Multistage model
$\hat{q}_0 = 0.1469$	$\hat{q}_0 = 0.1469$
$\hat{q}_1 = 0.009286$	$\hat{q}_1 = 0.009286$
	$\hat{q}_2 = 0.0$
	$\hat{q}_3 = 0.0$

sidered separately are listed in Table 8. We note that, in this case, the virtually safe doses from the combined data fell between those calculated for the males and females separately. It could also happen, and rightly so, that virtually safe doses from combined data sets could be larger than those calculated separately for any of the individual data sets. This could occur if both sets of data gave very nearly the same maximum likelihood estimate of the safe dose since a combination of the data sets would reduce the statistical variability about the common maximum likelihood estimate. This procedure thus permits the simultaneous use of the totality of the data from two or even more experiments with equally acceptable protocols in the calculation of virtually safe doses.

Computer programs have been developed to perform the calculations described in this paper. The program GLOBAL82 calculates the confidence

TABLE 8

Multistage virtually safe doses corresponding to 95% levels of confidence calculated from HCB hamster data

Extra risk	Males only	Females only	Males and females combined
10^{-4}	4.1×10^{-3}	8.5×10^{-3}	6.7×10^{-3}
10^{-5}	4.1×10^{-4}	8.5×10^{-4}	6.7×10^{-4}
10^{-6}	4.1×10^{-5}	8.5×10^{-5}	6.7×10^{-5}
10^{-7}	4.1×10^{-6}	8.5×10^{-6}	6.7×10^{-6}

bounds for a single data set in addition to performing several other data analysis functions described by Crump et al. [3]. A separate but similar program is available to calculate confidence bounds using several data sets simultaneously.

Parallel risk assessment procedures are available based upon the multistage model, but which utilize time-to-tumor information [7, 15, 16]. Whenever time-to-tumor data are available, an appropriate analysis based upon such data may be preferable to the use of crude dichotomous data as discussed in this paper. With time-to-tumor data, competing risks can be treated properly and more refined measures of risk can be estimated.

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