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Introduction

The issue addressed here is the application of a cost-effective procedure for reducing the total health risk of a mixture of toxic substances. One approach is to reduce exposure to all of the individual components within the mixture proportionately. This, however, may not be the most cost effective approach for reducing health risks. If it is possible to selectively reduce the health risks arising from individual components of a mixture of toxic substances, then an optimum strategy for cost effective reduction of the estimated total risk for the mixture can be determined. Such optimization could arise by selectively reducing particular classes of contaminants in a waste site, particular contaminants in air, water, food, or consumer products, and/or collecting better data to selectively reduce the estimates of upper limits of risk for individual components in a mixture.

An optimum strategy for reducing the total risk requires unbiased estimates of the individual component risks at low environmental exposure levels. This requires an accurate dose response model to predict low dose risks from high dose experimental data. Gaylor et al.[1] discuss conditions where unbiased low dose point estimates may be obtained. Often such estimates cannot be obtained. However, plausible upper bounds on low dose risk, upon which regulatory

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1 David W. Gaylor etl., *Point Estimates of Cancer Risk at Low Doses*, 14 Risk Anal. 843-850 (1994).

decisions are generally based, can be obtained. Therefore, this paper also considers a cost effective procedure for reducing the upper bound of the total estimated risk for a mixture of toxic substances.

Gaylor and Chen[2] provide a simple analytical function for the upper limit (L) of the estimate of risk for the sum of the risks of m components in a mixture

$$L = \sum P_i + \sqrt{\sum (L_i - P_i)^2} \quad (1)$$

where P_i and L_i are the point estimate and upper limit for the *i*th component in a mixture of m chemicals (i = 1, 2,..., m). Since the values of P_i are frquently near zero at low doses and the L_i values are generally much larger than those of P_i, eq.(1) may be approximated by

$$L = \sqrt{\sum L_i^2} \quad (2)$$

which is less than the traditional sum of the limits, ΣL_i. It is assumed here that, at low doses, antagonism and synergism are negligible and risks are approximately additive. Several authors have presented arguments for the additivity of cancer risks at low doses for mixtures of carcinogens: Brown and Chu,[3] Gibb and Chen[4] and Kodell et al.[5] If additivity of risks at low doses is not appropriate, more complex relationships would need to be employed.

The purpose of this paper is to examine the total estimated risk and the mathematical functions given in eq.(1) or (2) for the upper limits of risk for the sum of a mixture of chemicals as functions of cost in order to devise a cost efficient strategy for the reduction of risk estimates.

Strategy for the Reduction of the Estimated Total Risk

To develop a strategy for the optimum allocation of resources for reducing the estimate of risk for the sum of toxic components in a mixture, it is necessary to estimate individual risks at low doses and define the relationships between risk and the cost of achieving various

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2 David W.Gaylor, & James J. Chen, *A Simple Upper Limit for the Sum of the Risks of the Components in a Mixture,* 16 Risk Anal. 395-398 (1996).

3 Charles Brown,& Kenneth Chu, *Additive and Multiplicative Models and Multistage Carcinogenesis Theory*, 9 Risk Anal., 99-105 (1989).

4 Herman Gibb, & Chao Chen, *Multistage Model Interpretation of Additive and Multiplicative Carcinogenic Effects*, 6 Risk Anal. 167-170 (1986).

5 Ralph L. Kodell, Daniel Krewski, & Jan M. Zielinski, *Additive and Multiplicative Relative Risk in the Two-Stage Clonal Expansion Model of Carcinogenesis,* 11 Risk Anal. 483-490 (1991).

levels of risk for each individual component in a mixture. That is, the estimated risk (P_i) for the *i*th component must be expressed as a function of the cost (c_i) of achieving that level of risk, $P_i = f(c_i)$. It is desirable to determine the costs (c_i) devoted to reducing the estimated risk (P_i) for each component such that the total estimated risk $P = \Sigma P_i$ is minimized for a specified total cost $C = \Sigma c_i$. It is assumed here that, at low levels of risk, the risks are additive. The optimal strategy for minimizing P for a specified C is achieved when

$$\partial P_i / \partial c_i = \partial P_m / \partial c_m \qquad (3)$$

for all i = 1, 2,...m (See Appendix A), where ($\partial P_i / \partial c_i$) denotes the derivative of P_i with respect to c_i, which corresponds to the rate of change of the estimated risk at P_i per unit cost.

Strategy for the Reduction of the Upper Bound Estimate of Total Risk

In reducing the upper limit L in eq.(1), both the total estimated risk, ΣP_i, and the uncertainty, $[\Sigma (L_i - P_i)^2]^{1/2}$, are subject to reduction. To develop a strategy for the optimum allocation of resources for reducing the estimated upper limit of risk for the sum of the toxic components in a mixture, a relationship between the upper limit and the cost of achieving these upper limits must be established or assumed for each component. This relationship for the *i*th component in a mixture is denoted by a continuous function, $L_i = f_i(c)$, for all c > 0. It is desirable to determine the resources (c_i) devoted to reducing the upper limit of the risk estimate (L_i) for each component such that the estimated total limit (L) is minimized for a total specified cost of $C = \Sigma c_i$. The upper limit of the total estimated risk is minimized for a fixed cost, when

$$L_i / L_m = \frac{\left(\partial L_m / \partial c_m\right)}{\left(\partial L_i / \partial c_i\right)} \qquad (4)$$

where ($\partial L_i / \partial c_i$) is the derivative of L_i with respect to c_i and corresponds to the rate of change of the estimated upper limit at L_i per unit cost. Equivalently, the result in eq.(4) minimizes the total cost (Σc_i) needed to achieve a specified upper limit $[L = (\Sigma L_i^2)^{1/2}]$. The derivation of the optimization strategy expressed in eq.(4) is provided in Appendix B.

Hypothetical Example: Reduction of the Estimated Total Risk

Suppose the rate at which risk is reduced per unit cost is proportional to the size of the risk. That is, a specified cost is required to reduce the risk by a specified percent. The rate of change in the estimate of the risk at P_i per unit cost is proportional to P_i, which can be mathematically expressed as

$$\partial P_i / \partial c_i = -k_i P_i$$

where k_i is a constant. For example, consider a fixed cost which would reduce a given risk by half. Applying that cost twice would halve the risk again to one-fourth of its original value, etc., resulting in a negative exponential function

$$P_i = P_i' e^{-k_i c_i}$$

where P_i' is the initial value of the estimated risk.

For the above cost structure, let us suppose that the initial risks associated with a mixture were estimated to be $P_1' = 1 \times 10^{-4}$, $P_2' = 2 \times 10^{-4}$, and $P_3' = 3 \times 10^{-4}$. If it costs \$1M to reduce the risk of the first component (P_1) by half, then $P_1 = 0.5 \times 10^{-4}$ at $c_1 = 1$, and

$$0.5 \times 10^{-4} = 1.0 \times 10^{-4} e^{-k_1}$$

yielding $k_1 = 0.693$. Similarly, if it costs \$9M and \$3M to reduce both P_2 and P_3 by half, then, $k_2 = 0.077$ and $k_3 = 0.231$. From eq.(3), $P = \Sigma P_i$ is minimized for a fixed cost C when $(\partial P_i / \partial c_i) = (\partial P_m / \partial c_m)$, giving $k_i P_i = k_m P_m$ or $(P_i / P_m = k_m / k_i)$. That is, the optimum risks are inversely proportional to their respective rates of reduction. Supposing that \$10M are allotted to reduce the risk associated with this mixture, then $C = (c_1 + c_2 + c_3) = 10$. As shown in Appendix C, the optimum strategy is to use c_1 = \$2.274M to reduce P_1 to 0.207×10^{-4}; c_2 = \$0.904M to reduce P_2 to 1.866×10^{-4}; and \$6.822M to reduce P_3 to 0.620×10^{-4}. No smaller estimated total risk would result from any alternate allocation of the \$10M.

In the above example, the largest effort should be allocated to reducing the largest (P_3') contributor to the initial estimated risk. Although the second component had a larger initial risk than the first, fewer dollars should be allocated to reducing the estimated risk of the second component because its rate of risk reduction per unit cost, k_2, is much lower than k_1. A summary of this example is given in Table 1.

The estimated total risk of 2.693×10^{-4} is the lowest that can be achieved given a total allotment of \$10M. Similarly, optimum solutions for other total costs could be calculated or the minimum cost to achieve a specified level of total estimated risk, e.g., $P = 1 \times 10^{-5}$, could be calculated.

Obviously, a different cost structure would yield a different result. The intent here is only to use a specific cost structure to illustrate a general approach for efficient reduction of the total estimated risk, rather than propose a particular cost structure.

Table 1

Summary of Results of Estimated Risk Calculations for the Hypothetical Example

Component	*Initial Risk Estimate*	*Rate of Risk Reduction*(k)	*Optimum Cost*(\$M)	*Optimum Risk Estimates*
1	1×10^{-4}	0.693	2.274	0.207×10^{-4}
2	2×10^{-4}	0.077	0.904	1.866×10^{-4}
3	3×10^{-4}	0.231	6.822	0.620×10^{-4}
Total	6×10^{-4}		10.000	2.693×10^{-4}

Except in the unlikely event that $k_i = k_m$ for all m components in the mixture, the optimum solution would generally not be to reduce the estimated risk of all the components in a mixture to the same level, e.g., $P = 10^{-6}$.

Hypothetical Example — Reduction of the Upper Bound Estimate of Total Risk

To illustrate, suppose that the estimated upper limit of risk is reduced by a constant factor for each unit cost. This type of cost relationship is described by the derivative $(\partial L_i/\partial c_i) = -k_iL_i$ which yields the negative exponential function

$$L_i = L_i' e^{-k_i c_i} \qquad (5)$$

where L_i'. is the current estimate of the upper limit of risk for the *i*th component of a mixture with the additional funds spent, $c_i = 0$, and k_i is determined from cost considerations. For example, if the upper limit estimate of risk can be halved with a cost of c_i = \$1M, $L_i = L_i'/2$, from eq.(5)

$$L_i'/2 = L_i' e^{-k_i}$$

and $k_i = -\ln(1/2) = 0.693$.

The partial derivative of L_i with respect to c_i is $(\partial L_i/\partial c_i) = -k_i L_i$. From eq.(4), the optimum solution is to allocate funds such that

$$L_i / L_m = \sqrt{k_m / k_i} \qquad (6)$$

As shown before, this allocation also minimizes the cost necessary to achieve a specified value of L. Reducing the estimated upper limits of risk of the components in a mixture in a manner inversely proportional to the square root of their relative rates of reduction per unit cost provides the optimum solution.

For upper limits that are a linear function of dose

$$L_i = q_{i1}^* d_i \qquad (7)$$

such as often used for cancer risk estimates, eq.(6) can be written as

$$d_i / d_m = q_{m1}^* / q_{i1}^* \sqrt{k_m / k_i} \qquad (8)$$

If the relative doses in the mixture can be adjusted to satisfy eq.(8), the total cost of risk reduction is minimized where the upper limits of risk are reduced exponentially by c_i dollars allocated to the *i*th component as described by eq.(5). This applies only where it is possible to selectively reduce the uncertainty of risk for any or all of the components in a mixture. This result could be used to provide an optimum strategy for the reduction of exposures to individual components which are produced by different sources.

An examination of eq.(6) shows that the common goal of reducing the upper limits of risk for each of the components in a mixture to the same level, e.g., 10^{-6}, would only be optimum in the unlikely event that $k_i = k_m$ for all of the m components of a mixture.

Again, the intent here was not to propose this particular cost structure, but to illustrate the general approach for efficient risk (cost) reduction through the use of a specific type of relationship between the upper bound estimate of risk and cost.

Discussion and Summary

In the case of a mixture of *m* toxic chemicals, an upper limit of the total estimated risk has been traditionally calculated conservatively by $L = \Sigma L_i$. Gaylor and Chen[6] have shown that a less conservative and more accurate upper limit is given by

$$L = \sum P_i + \sqrt{\sum (L_i - P_i)^2}.$$

Slob[7] and Bogen[8] have shown that if the P_i values are normally distributed and the L_i are upper $(1-\alpha) \times 100\%$ confidence limits, L is an upper $(1-\alpha) \times 100\%$ confidence limit for the sum of the risks in a mixture. Where the L_i values are generally several times larger than those of P_i, a simple approximation is provided by

$$L = \sqrt{\sum L_i^2}.$$

When it is possible to selectively reduce one or more contaminants in a mixture, an optimum strategy can be used to reduce the sum of the estimated risks where a relationship between the risk and cost of reduction of the components in a mixture can be established. This is accomplished by minimizing the total estimated risk for a given total cost, assuming additivity of risks. The same relative reductions are obtained by minimizing the costs subject to a desired estimate of the sum of the risks. The same procedure can be used to determine an optimum strategy for reducing the estimate of the upper limit of the sum of the risks.

In general, reducing the estimated risks or upper limits to a common level, e.g., 10^{-6}, is not optimum. Instead, the optimum strategy for risk reduction of a mixture depends upon both the relative sizes of the individual estimates of the initial component risks or upper limits and the relative rates at which they can be reduced per unit cost. Obviously, the results are no more accurate than the cost assumptions used, but the minimization approach can provide some guidance in the effective usee of funds for reducing the sum of estimated risks or the upper limit of the sum of risk estimates for mixtures of chemicals.

6 Gaylor, & Chen, *supra* note 2.

7 Werner Slob, *Uncertainty Anal. in Multiplicative Models*, 14 Risk Anal. 571-576 (1994).

8 Kenneth T. Bogen, *A Note on Compounded Conservatism*, 14 Risk Anal. 379-381 (1994).

Appendix A

The derivation of the optimum strategy for the reduction of the estimated total risk follows. The estimated risk (P_i) for the *i*th component must be expressed as a function of the cost (c_i) of achieving that level of risk, $P_i = f(c_i)$. It is desired to determine the costs (c_i) devoted to reducing the estimated risk (P_i) for each component such that the total additive estimated risk, $P = \Sigma P_i$, is minimized for a specified total cost of $C = \Sigma c_i$.

This is achieved by minimizing

$$P = \Sigma P_i + \lambda (C - \Sigma c_i).$$

Note that $(C - \Sigma c_i) = 0$ and λ is a constant LaGrange multiplier. The partial derivative of P with respect to c_i is

$$\partial P / \partial c_i = \partial P_i / \partial c_i - \lambda.$$

The value of P is minimized where $(\partial P_i / \partial c_i) = 0$. That is, where all $(\partial P_i / \partial c_i) = \lambda$. That implies $(\partial P_i / \partial c_i) = (\partial P_m / \partial c_m)$ for all i = 1, 2, ..., m. A unique mathematical solution may not exist. In such cases, a numerical evaluation and computer search could be used to find the combination of c_i's, that minimize $P = \Sigma P_i$ for a given cost of $C = \Sigma c_i$.

Similarly, the problem can be stated such that it is desirable to determine the values of c_i such that the total cost $C = \Sigma c_i$ is minimized subject to risk reduction to a specified level of $P = \Sigma P_i$.

This is achieved by minimizing

$$C = \Sigma c_i + \gamma (P - \Sigma P_i).$$

Note that $(P - \Sigma P_i) = 0$ and γ is a constant. The partial derivative of C with respect to P_i is

$$\partial C / \partial P_i = \partial c_i / \partial P_i - \gamma.$$

The minimum is achieved where $(\partial C / \partial P_i) = 0$, giving $(\partial c_i / \partial P_i) = \gamma$, or $(\partial c_i / \partial P_i) = (\partial c_m / \partial P_m)$, or $(\partial P_i / \partial c_i) = (\partial P_m / \partial c_m)$ as before. Thus, the same solution is obtained whether P is minimized for a fixed C, or C is minimized for a fixed P.

Appendix B

The following is a derivation of the optimum strategy for reducing the upper bound estimate of the total risk. The goal is to determine the allocation of resources having cost (c_i) in order to reduce the upper limit of the risk estimate (L_i) for each component, such that the estimated total limit, $L = (\Sigma L_i^2)^{1/2}$, is minimized for a total specified total cost of $C = \Sigma c_i$. This is accomplished by minimizing $[L + \lambda (C - \Sigma c_i)]$, where λ is the constant LaGrange multiplier and $(C - \Sigma c_i) = 0$. From eq.(2), L can be approximated by $(\Sigma L_i^2)^{1/2}$ when the values of L_i are much larger than those of P_i. The partial derivative of

$$L = [(\Sigma L_i^2)^{1/2} + \lambda (C - \Sigma c_i)]$$

with respect to c_i is

$$\partial L_i / \partial c_i = L_i (\Sigma L_i^2)^{-1/2} (\partial L_i / \partial c_i) - \lambda.$$

The minimum value of L is achieved where the partial derivatives equal zero, i.e., $L_i (\partial L_i / \partial c_i) = \lambda L$. Hence, $L_i(\partial L_i / \partial c_i) = L_m(\partial L_m / \partial c_m)$ for all i = 1, 2, ..., m. Equivalently, this solution minimizes the total cost, $C = \Sigma c_i$, to achieve a specified upper limit of L.

Appendix C

The optimum solution for reduction of the total estimated risk is achieved when $P_i / P_m = k_m / k_i$.

Hence,

$$P_1 / P_3 = k_3 / k_1 = 0.231/0.693 = 1/3, \text{ and}$$

$$P_2 / P_3 = k_3 / k_2 = 0.231/0.077 = 3.$$

For P_1/P_3, $[(1 \times 10^{-4} e^{-0.693c_1})/(3 \times 10^{-4} e^{-0.231c_3})] = 1/3$, yielding $c_1/c_3 = 1/3$. For P_2/P_3, $[(2 \times 10^{-4} \times e^{-0.077c_2})/(3 \times 10^{-4} \times e^{-0.231c_3})] = 3$, yielding $(-.077c_2 + .231c_3) = \ln(4.5) = 1.504$. Suppose \$10M is to be used to reduce the risk of this mixture, i.e., $c_1 + c_2 + c_3 = 10$. Solving these three equations for the three individual costs gives c_1 = \$2.274M, c_2 = \$.904M, and c_3 = \$6.822M, with risks $P_1 = .207 \times 10^{-4}$, $P_2 = 1.866 \times 10^{-4}$, and $P_3 = .620 \times 10^{-4}$, for a total risk $\Sigma P_i = 2.693 \times 10^{-4}$. Assuming that the riska are additivie, no other allocation of the \$10M would result in a smaller total estimated risk.