Monte Carlo Results for the 3-Poly Test for Animal Carcinogenicity Experiments

Wai-Yuan Tan and Jane Honyuang Zhang

Department of Mathematical Sciences, University of Memphis, Memphis, TN 38152 USA

By using a two-stage model of carcinogenesis, we generated Monte Carlo studies to assess the efficiency and robustness of the 3-poly test for animal carcinogenicity experiments. The Monte Carlo results indicate that the 3-poly test is quite powerful for detecting the carcinogenic effects of complete carcinogens, moderate promoters, and initiators with moderate or large effect, but, in some cases, it is less powerful for weak initiators or weak promoters. As expected, the 3-poly test is insensitive to the toxicity of many agents. Key words: carcinogenicity experiment, initiator, Monte Carlo, 3-poly test, promoter, toxicity, two-stage model. Environ Health Perspect 104:872–877 (1996)

To assess risk of environmental agents by animal carcinogenicity experiments in the past, statisticians would carry out trend tests to determine if the agents were carcinogenic. One well-known carcinogenicity test is the Armitage-Cochran test (1,2). Portier and Bailer (3) pointed out that such tests are subjected to serious biases when agents are toxic or when there are causes of death other than cancer. To correct for such biases, Portier and Bailer (3) have proposed a 3-poly test based on the classical Armitage-Doll model of carcinogenesis. Because the Armitage-Doll cancer model does not take proliferation of intermediate cells into account [see Tan (4)], one may wonder if the method is robust and efficient under other realistic models of carcinogenesis. To answer these questions, we generated Monte Carlo studies of this test by using a two-stage model of carcinogenesis as described by Moolgavkar and Knudson (5).

The basic reason we used this model is that it has strong biological support [see Tan (4)]. Because the two-stage model and its extensions are complex enough to involve stochastic proliferation and differentiation of initiated and cells and yet simple enough to be applicable to many data sets, this model has been suggested as the basic model for assessing risk of environmental agents (6).

We will briefly describe the model and how Monte Carlo data can be generated; we will then apply the 3-poly methods to the data. To assess the efficiency and robustness of the test, we will compute the Monte Carlo size and the power of the test. Finally, we will discuss the results and some of the issues relevant to the method.

The Model and Generation of Monte Carlo Data

To generate Monte Carlo data from such an experiment, we assign D as the random variable for the time to death. As the random variable for the time to the onset of cancer tumors, and Z as the variable for the dose level. Given Z = z, let α0(t|z), β0(t|z), (s ≥ 0), and λ0(t|z) be the incidence functions of death without cancer, death with cancer being developed at s, and cancerous tumors, respectively. Then,

\[ \alpha_0(t|z) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P_t \{ D \in [t, t + \Delta t] | D \geq t, T \geq t, Z = z \} \]

\[ \beta_0(t|z) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P_t \{ D \in [t, t + \Delta t] | D \geq t, T \geq t, Z = z \} \]

\[ \lambda_0(t|z) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P_t \{ T \in [t, t + \Delta t] | D \geq t, T \geq t, Z = z \} \]

For \( j \leq t < j+1 \), the survival functions associated with \( \alpha_j(t|z) \), \( \beta_j(t|z) \), and \( \lambda_j(t|z) \) are given respectively by

\[ A_j(t) = \exp \left\{ -\int_0^t \alpha_0(s|z) ds \right\} \]

\[ = \exp \left\{ -\sum_{j=1}^m \alpha_j(t) - \int_0^t \alpha_0(s|z) ds \right\} \]

\[ B_j(t) = \exp \left\{ -\int_0^t \beta_0(s|z) ds \right\} \]

\[ = \exp \left\{ -\sum_{j=1}^m \beta_j(t) - \int_0^t \beta_0(s|z) ds \right\} \]

for \( j > i \), and

\[ \Lambda_j(t) = \exp \left\{ -\int_0^t \lambda_0(s|z) ds \right\} \]

\[ = \exp \left\{ -\sum_{j=1}^m \lambda_j(t) - \int_0^t \lambda_0(s|z) ds \right\} \]

where \( \alpha_j(t) = \int_{t-1}^t \alpha_0(s|z) ds, \beta_j(t) = \int_{j-1}^j \beta_0(s|z) ds \) for \( j > i \), and \( \lambda_j(t) = \int_{j-1}^j \lambda_0(s|z) ds \).

Assume that \( \beta_j(t|z) = \beta_0(t|z) \) for \( j \leq t < j+1 \) and that during one unit time, the event of death and the event of developing cancerous tumors are independent of each other. Then \( \beta_j(t|z) = \beta_0(t|z) \) for \( j \leq t < j+1 \), and the probabilities for generating \( a_j(t|z) \), \( a_j(t|z) \), \( b_1(z) \), and \( b_2(z) \) are given respectively by

\[ P_j(t|z) = P_t \{ D \in [j-1, j] | T < j+1, z \} = [A_j(t) - A_{j-1}(t)] \Lambda_j(t) \]

\[ P(t|z) = P_t \{ D \in [j-1, j] | T < j+1, Z = z \} = [A_j(t) - A_{j-1}(t)] \Lambda_j(t) \]

Address correspondence to W. Y. Tan, 8031 Brookie Cove, Germantown, TN 38138 USA. Received 14 November 1995; accepted 10 April 1996.
Theorem 1. With \( P_1(j|z) \), \( P_2(j|z) \), \( P_3(z) \), and \( P_4(z) \), as given above, one has

\[
P_3(z) + P_4(z) + \sum_{j=1}^{N_0} [P_1(j|z) + P_2(j|z)] = 1
\]

Proof. Let \( P_3(j|z) \) and \( P_4(j|z) \) be obtained from \( P_3(z) \) and \( P_4(z) \), respectively, by replacing \( t_i = t_{i+1} \) by \( t_i \). Note that \( B_j(j) = 1 \) for \( j=2, 3, \ldots, t_i = t_{i+1} \)

It follows that

\[
P_3(M|z) + P_4(M|z) + \sum_{j=1}^{N_0} [P_1(j|z) + P_2(j|z)]
\]

where \( N_0(t) \) is the number of normal stem cells in the cell division stage at time \( t \).

For the proof of Equation 11 and for the general theory of two stage models of carcinogenesis, see Tan (4), chapter 3.

Note that \( N_0(t) = N_0 f_j(t) \), where \( N_0 \) is the total number of normal stem cells at time \( 0 \), and where \( f_j(t) \) is the density of first passage time to the cell division stage at time \( t \) for normal stem cells at time \( 0 \).

Let \( b(t|z) \) and \( d_1(t|z) \) denote the birth rate and death rate at time \( t \) of initiated cells for animals exposed to the carcinogen with dose level \( z \). Suppose that \( b(t|z) = b(t) \), \( d_1(t|z) = d_1(t) \), \( v_1(t|z) = v_1(t) \), and \( v_2(t|z) = v_2(t) \), then \( v_1(t|z) \) and \( v_2(t|z) \) are independent of time \( t \). Then

where

\[
\lambda_0(t|z) = \frac{\lambda_0(t)}{\lambda_0(t) + \lambda_0(t-1)}
\]

and

\[
G_j(g) = \int_{0}^{\infty} g(t|z) \lambda_0(t|z) dt
\]

The Two-stage Model of Carcinogenesis

Let \( \lambda_1(t|z) \) and \( \lambda_2(t|z) \) denote the mutation rates at time \( t \) of the first and second event, respectively, for animals exposed to the carcinogen with dose level \( z \). Let \( \phi(z, t_1, t_2) = \phi(t_1, t_2) \) be the probability generating function of the number of initiated cells (I cells) and cancerous tumor cells (T cells) at time \( t \) given one initiated cell arising from a normal stem cell at time \( s \). The two-stage model of carcinogenesis specifies that

where \( A(t) = A(t) \)

and

\[
\lambda_2(j|z) = \int_{0}^{\infty} \lambda_2(t|z) dt = G_j(g) - G_j(g-1)
\]

and

\[
G_j(g) = \int_{0}^{\infty} \lambda_2(t|z) dt
\]

Given \( \alpha_0(t|z) \), \( \beta_0(t|z) \), and \( \lambda_0(t|z) \), by Theorem 1 one may readily generate observed numbers of \( a_0(j|z) \), \( a_1(j|z) \), \( b(t) \), and \( d_1(t) \) by computer. A simple algorithm for generating these observed numbers is given in the Appendix.

\[
\text{It follows that for the homogeneous model in which}
\]

\[
\lambda_1(t|z) = \int_{0}^{\infty} \lambda_1(t|z) dt = G_j(g) - G_j(g-1)
\]

and

\[
\lambda_2(t|z) = \int_{0}^{\infty} \lambda_2(t|z) dt
\]

where

\[
\phi(t) = \left[ \phi_1(t) + \phi_2(t) \right] + v_2(t)
\]

and

\[
\phi_2(t) = \left[ \phi_1(t) + \phi_2(t) \right] + v_2(t)
\]

and

\[
\phi_1(t) = \left[ \phi_1(t) + \phi_2(t) \right] + v_2(t)
\]

and

\[
\phi_2(t) = \left[ \phi_1(t) + \phi_2(t) \right] + v_2(t)
\]

where \( \Delta(z) = N_0 \lambda_1(t) v_2(t) / [\phi_1(t) 1 + \phi_2(t)] \)

Environmental Health Perspectives • Volume 104, Number 8, August 1996
The 3-Poly Test
To adjust for toxicity and effects on survival of the agents, Baier and Portier (7) and Portier and Baier (3) proposed a 3-poly test to determine if the agents are carcinogenic. The first step of this test is to compute the weight \( \omega_j \) for each animal and adjust the estimates of quantal response by using this weight. A modified \( \chi^2 \)-test is then derived by substituting the adjusted estimates of quantal response into the Cochran-Armitage trend test. Specifically, the procedure is given in the following steps.

If \( \omega_j \) is the weight for the \( j \)th animal in the group of animals exposed to the carcinogen with dose level \( d_j \) and \( t_{ij} \) is the time of death including sacrifice of this animal, then based on the Armitage-Doll multistage model, Baier and Portier (7) derived \( \omega_j = \omega(t_{ij}) \) where \( t_{ij} \) is the termination time of the experiment. For practical purposes, \( k \) was taken as 3, thus giving the terminology of the 3-poly test.

If \( \delta_j \) is the indicator function defined by \( \delta_j = 1 \) if the animal died (including sacrifice) with tumors at \( t_j \) and \( \delta_j = 0 \) if the animal died without tumors at \( t_j \), and \( n_j \) is the number of animals in the group exposed to the carcinogen with dose \( d_j \), then the adjusted estimate of the quantal response to the dose level \( x(z) = \sum_{j=1}^{n} \delta_j \omega_j \), where

\[
x^{(0)}_j = \sum_{j=1}^{n} \delta_j \omega_j \quad \text{and} \quad m^{(0)}_j = \sum_{j=1}^{n} \omega_j,
\]

On substituting the adjusted estimates of the quantal response into the Cochran-Armitage trend test, Portier and Baier (3) derived the following \( X^2 \) statistic:

\[
X^2 = \left[ \frac{M^{(0)}_j}{M^{(0)} - X^{(0)}_j} \right] \left[ \frac{\sum_{i=0}^{l} (x^{(0)}_j - x^{(0)}_j) x^{(0)}_j}{\sum_{i=0}^{l} (x^{(0)}_j - x^{(0)}_j)^2} \right] \left[ \frac{\sum_{i=0}^{l} x^{(0)}_j x^{(0)}_j}{\sum_{i=0}^{l} x^{(0)}_j} \right] \left[ \frac{\sum_{i=0}^{l} x^{(0)}_j - \sum_{i=0}^{l} x^{(0)}_j x^{(0)}_j}{\sum_{i=0}^{l} x^{(0)}_j} \right] \left[ \frac{\sum_{i=0}^{l} x^{(0)}_j}{\sum_{i=0}^{l} x^{(0)}_j} \right]
\]

(17)

where \( M^{(0)}_j = \sum_{i=0}^{l} m^{(0)}_j X^{(0)}_j = \sum_{i=0}^{l} \omega_j x^{(0)}_j \) and \( x^{(0)}_j = 0, 1, \ldots, l \) are the dose levels.

Thus, one rejects the null hypothesis at level \( \alpha \) to conclude that the agent is carcinogenic if \( X^2 \geq \chi^2(1, \alpha) \) where \( \chi^2(1, \alpha) \) is the upper \( \alpha \% \) of the \( \chi^2 \) distribution with one degree of freedom. The \( p \)-value of the test is the probability that \( X^2 \geq X^2 \) where \( X^2 \) denotes a \( \chi^2 \) distribution with one degree of freedom.

Portier and Baier (3) obtained the \( p \)-values for the Cochran-Armitage trend test and for the modified Cochran-Armitage test as 0.528 and 0.034, respectively. Thus, the Cochran-Armitage trend test failed to detect the carcinogenicity of the agent, but the modified test indicated that the chemical is carcinogenic at the significant level 0.05. This result suggests the usefulness of the modified test.

Generation of Monte Carlo Studies
In this section we will assume some parameter values and use the model to generate Monte Carlo data to assess the efficiency and robustness of the 3-poly test. To illustrate the results, we will assume four dose levels \( a = 0, 25, 50, \) and 100.

Selection of Parameter Values
To make the model more realistic, we will select the parameter values from estimates in published papers and discuss these parameters below.

Survival parameters. Because Portier et al. (8) have shown that the survival functions of Fischer rats are best fitted by the modified Weibull model, we chose the incidence of death without tumors by

\[
\alpha_s(t) = \left( 1 + \alpha_s \right) \left( \alpha_1 + \alpha_2 z \right)^{a_s-1}
\]

(18)

Note that the above values of \( \alpha_s \) were estimates by Portier et al. (8) on Fischer rats. If \( \alpha_s = 0 \), then \( \alpha_s \) is independent of \( x \) so that the carcinogen has no toxic effects on the survival of animals. Thus \( \alpha_s \) provides a measure of the toxicity of the carcinogen.

Following Baier and Portier (7), we assume that the incidence of death with cancer tumors being developed during \([t-1, t)\) is

\[
\beta_s(t) = (1 + \beta_s) \left\{ \beta_1(t-1) + \beta_2 \left[ \beta_3(t-1) + \beta_4(t-1)^2 \right] \right\} + \phi_2 \beta_3(t-1)^2 t_M
\]

(19)

where \( \phi_2 = 2 \) and \( \delta = 1.2 \).

The parameters of growth of tumor cells. Following Tan and Chen (9), we assume that for each tumor cell arising at time \( t \), the probability that this tumor cell will divide for the first time during \([t+ \Delta t] \) is \( \gamma(t) \Delta t + o(\Delta t) \). Given that a tumor cell divides during \([t+ \Delta t] \), we assume that it either divides at the end of cell turnover this tumor cell either gives rise to two tumor cells with probability \( \alpha_s(t) \) or dies with probability \( \beta_s(t) \). For the Monte Carlo studies, we assume that \( \gamma(t) = \gamma \), \( \alpha_s(t) = \alpha_s \), and \( \beta_s(t) = \beta_s \). Then, as shown in Tan and Chen (9), the probability that a tumor cell at time \( t \) will eventually develop into a cancerous tumor is given by \( q = 1 - (\beta_s/\alpha_s) \). For the generation of data, we take \( q = 0.80 \).

Cancer parameters. Because mutations take place only during cell division, we will follow Chen and Farland (10) to assume that for mutations, cell proliferation, and differentiation to take place, cells must first enter into the division stage from the resting stage. Let \( f_1(t) = \beta_s(t) \) be the probability density of the first passage of time from the resting stage at \( t_0 \) to the cell division stage at time \( t \) for normal stem cells. Let \( f_2(t) = \beta_s(t) \) be the mutation rate at time \( t \) of normal stem cells. Then, to order \( \alpha_s(t) \), \( v_1(t) \) is the probability of giving rise to one normal stem cell and one initiated cell, given cell division of a normal stem cell during \([t+ \Delta t] \). Furthermore, to order \( \alpha_s(t) \), \( N_0 f_1(t) \) is the average number of new initiated cells arising from normal stem cells during \([t+ \Delta t] \) given \( N_0 \) normal stem cells at time \( t_0 \). For generating Monte Carlo data, we take \( N_0 = 10^7 \) and assume \( f_1(t) \) as a gamma density with the mode at time 13 and with a scale parameter \( \alpha_s = 16.5 \).

To model the proliferation and mutation of I cells, we followed Chen and Farland (10) to assume that for animals exposed to the carcinogen with dose level \( z \), the probability that each I cell will divide during \([t+ \Delta t] \) is \( \gamma(t) \Delta t + o(\Delta t) \). Given that an I cell divides during \([t+ \Delta t] \), we assume that at the end of cell turnover, this I cell will either give rise to two I cells with probability \( \alpha_s \), one I cell and one tumor cell with probability \( \beta_s \), or die with probability \( v_1 = 1 \). Then, as shown in Tan and Chen (9),

\[
\phi_1(z) = \gamma(t) \alpha_s \omega
\]

(20)

and

\[
\phi_2(z) = \left[ \omega - (\alpha_s - \beta_s + v_1)/(2\omega) \right]
\]

(21)

where

\[
\omega = \left[ (\alpha_s + \beta_s + v_1)^2 - 4\alpha_s \beta_s \right]^{1/2}
\]

(22)
and

\[ q = 1 - \frac{\beta_T}{\alpha_T} \]  

(23)

For the generation of Monte Carlo data, we take \( \gamma_1 = 1 - e^{-0.15} \), \( \gamma_2 = 0 \), 0.5, 1, 2, \( \alpha_0 = 0.52 \), \( \beta_0 = 0.47999 \), and \( v_1 = 10^{-7} \) with \( q = 0.8 \). Note that if \( \gamma_1 = 0 \) then \( \gamma_1(z) = \gamma_2 \) is independent of \( z \) so that the carcinogen has no effects on the proliferation of the cells. It follows that \( \gamma_1 \) provides a measure for the increased proliferation of I cells due to the action of the carcinogen. We will thus use \( \gamma_1 \) as a measure for the promoting effects of the carcinogen.

Finally, for the mutation rates, we take \( v_1(z) = 10^{-7} \). Also, we follow Moolgavkar et al. (11) to assume \( v_2(z) = \mu_{10}^{0.01\log(1+z)} \). For generation of data, we take \( \mu_{10} = 10^{-7} \), \( \theta_{12} = 0.1 \), and 0.92. Note that if \( \theta_{12} = 0 \), then \( v_2(z) = \mu_{10}^{0.01} \) is independent of \( z \). It follows that \( \theta_{12} \) provides a measure for the increased mutation rate over the spontaneous rate due to the action of the carcinogen. Thus we will use \( \theta_{12} \) as a measure for the initiating effects of the carcinogen.

With the parameter value given above, we have used the Monte Carlo model to generate independent random samples. For each random sample, we assume four dose levels 0, 25, 50, and 100; the sample size is assumed to be 50 to comply with the sample size given by the example in Bailer and Portier (7). Five hundred independent random samples were generated under each condition. The Monte Carlo p-values for the case in which \( f(x) \) is a gamma density are shown in Table 1. The corresponding Monte Carlo p-values in the case \( f(x) = 1 \) are shown in Table 2.

The following observations are made from the results of Tables 1 and 2:

- If \( \gamma_1 > 0 \) and \( \theta_{12} > 0 \) so that the carcinogen is a complete carcinogen (i.e., both an initiator and promoter), then the 3-poly test appears to be quite powerful in detecting the carcinogenic effects of the agent in question.

- If \( \gamma_1 > 0 \) is moderate or large so that the carcinogen is a promoter with moderate or large effect, the 3-poly test is quite powerful in detecting the carcinogenic effects of the agent in question, even though the effect of an initiator is very small. On the other hand, if \( \theta_{12} = 0 \) and \( \gamma_1 > 0 \) is small so that the carcinogen is a weak promoter without the presence of an initiator, then the 3-poly test may not be a powerful test for detecting the carcinogenic effect of the agent unless the toxicity of the agent is not strong or the proliferation rate of the normal stem cells is zero (i.e., \( f(x) = 1 \)). In any case, however, the 3-poly test is at least as good as the Armitage-Cochran test. This is expected since the Armitage-Cochran test may not detect the carcinogenic effects of the chemical, even in situations in which the carcinogen is a promoter with moderate effect, due to the toxicity of the agent.

- If \( \theta_{12} > 0 \) is moderate or large so that the carcinogen is an initiator with moderate or large effect, the 3-poly test is quite powerful in detecting the carcinogenic effects of the agent in question, regardless of whether a promoter is present or not. On the other hand, if \( \gamma_1 = 0 \) and \( \theta_{12} > 0 \) is small so that the carcinogen is a weak initiator without the presence of promoting agents, then in some cases, the p-values can be very small, depending on the toxicity of the agent. In these cases, the 3-poly test may not be a powerful test for detecting the carcinogenic effects of the agent. In any case, however, the 3-poly test is at least as powerful as the Armitage-Cochran test, which is expected because the Armitage-Cochran test may not detect the carcinogenic effects of the agent, even in situations in which the carcinogen is an initiator with moderate effect, due to the toxicity of the agent.

- From Tables 1 and 2, we observe that when \( H_0 \) is true (i.e., the agent is not carcinogenic), the probability (p-values) of rejecting \( H_0 \) ranges from 0.0001 to 0.09. Furthermore, this probability is less than 0.05 only when there is high toxicity (in this case, there were probably few tumor responses). These results suggest that at the 0.05 level, \( H_0 \) may be rejected even though \( H_0 \) is true. Note that \( H_0 \) is true if, and only if, \( \gamma_1 = 0 \) and \( \theta_{12} = 0 \). Thus, if \( H_0 \) is true, the proliferation rate of the I cells is the same over different dose levels, and the mutation rate from normal stem cells to I cells equals the spontaneous rate of this mutation, regardless of whether the carcinogen is present.

- Results in Tables 1 and 2 indicate that the decision reached by the 3-poly test is quite robust with respect to the toxicity of the carcinogen. This suggests that the 3-poly test has achieved its intended purpose for adjusting the toxicity effects of the agent.

### Table 1. The Monte Carlo p-values of the 3-poly test when \( f(x) = 1 \)

| Initiator | Promoter Promoter | Monte Carlo p-value |
|-----------|--------------------|---------------------|
| \( \theta_{12} \) | \( \gamma_1 \) \( \gamma_2 \) | \( \phi \) |
| 0.00 | 0.00 | 0.00 | 0.0540 |
| 0.00 | 0.00 | 4.00 | 0.000001 |
| 0.00 | 0.50 | 0.00 | 0.3080 |
| 0.00 | 0.50 | 1.00 | 0.9380 |
| 0.00 | 1.00 | 0.00 | 0.8300 |
| 0.00 | 1.00 | 1.00 | 1.0000 |
| 0.10 | 0.00 | 0.00 | 0.1060 |
| 0.10 | 0.00 | 1.00 | 0.4900 |
| 0.10 | 0.00 | 4.00 | 0.3940 |
| 0.10 | 0.50 | 0.00 | 0.7640 |
| 0.10 | 0.50 | 1.00 | 1.0000 |
| 0.10 | 1.00 | 0.00 | 0.9520 |
| 0.10 | 1.00 | 1.00 | 1.0000 |
| 0.20 | 0.00 | 1.00 | 0.1000 |
| 0.20 | 0.50 | 0.00 | 0.9880 |
| 0.20 | 0.50 | 1.00 | 1.0000 |
| 0.92 | 0.50 | 4.00 | 1.0000 |

### Table 2. The Monte Carlo p-values of the 3-poly test when \( f(x) = 1 \)

| Initiator | Promoter Promoter | Monte Carlo p-value |
|-----------|--------------------|---------------------|
| \( \theta_{12} \) | \( \gamma_1 \) \( \gamma_2 \) | \( \phi \) |
| 0.00 | 0.00 | 0.00 | 0.0620 |
| 0.00 | 0.00 | 1.00 | 0.0960 |
| 0.00 | 0.50 | 0.00 | 0.2700 |
| 0.00 | 0.50 | 1.00 | 0.8280 |
| 0.00 | 1.00 | 0.00 | 0.2040 |
| 0.00 | 1.00 | 1.00 | 1.0000 |
| 0.10 | 0.00 | 0.00 | 0.0720 |
| 0.10 | 0.00 | 1.00 | 0.2480 |
| 0.10 | 0.50 | 0.00 | 0.0620 |
| 0.10 | 0.50 | 1.00 | 0.9980 |
| 0.10 | 0.50 | 4.00 | 0.9960 |
| 0.10 | 1.00 | 0.00 | 0.9320 |
| 0.10 | 1.00 | 1.00 | 1.0000 |
| 0.92 | 0.50 | 0.00 | 0.9980 |
| 0.92 | 0.50 | 1.00 | 1.0000 |
| 0.92 | 0.50 | 4.00 | 1.0000 |
| 0.92 | 1.00 | 0.00 | 1.0000 |
| 0.92 | 1.00 | 1.00 | 1.0000 |
| 0.92 | 1.00 | 4.00 | 1.0000 |

Conclusions and Discussion

To adjust for the toxic effects or competing death from the carcinogen, Bailer and Portier (10) and Portier and Bailer (3) have proposed a 3-poly test to determine the carcinogenic effects of the agent. Because this test is based on the classical Armitage-Doll model of carcinogenesis and because the latter model does not take into account the cell proliferation of the normal stem cells and the intermediate cells (initiated cells) and is not supported by modern cancer biology [see Tan (4)], one may wonder how the 3-poly test would perform under some real situations. To answer these questions, we have generated Monte Carlo studies by using the two-stage model of carcinogenesis. The main reason that we chose the two stage model is that it has strong biological

Environmental Health Perspectives • Volume 104, Number 8, August 1996 875
Appendix

This subroutine generates the number of animals that died without tumor (E1), the number of animals that died with tumor (E2), the number of terminal sacrifices without tumor (E3), and the number of terminal sacrifices with tumor (E4), given the survival functions and the probabilities.

SUBROUTINE ZA2(Z,theta,alpha,gamma, E1,E2,E3,E4,iseed)
INTEGER Z,J,K,ISEED,E1(130),E2(130),E3,E4,NOUT
REAL*8 P1(130),P2(130),P3,P4,U,S,A,G,r
REAL*8 theta, gamma, phi_0,alpha
DIMENSION S(1:130),A(1:130),G(1:130,1:130)
DIMENSION U(0:130)
EXTERNAL PZ,SAG,RNSET,RNGET,DRNUN,UMACH

Compute the survival functions A(i) for death without cancer, G(i,j) for death with cancer, and S(i) for cancer development.

CALL PZ(Z,theta, alpha, gamma, S,A,G)

Compute the probabilities P1(i) for death without cancer, P2(i) for death with cancer, P3 for sacrifice without cancer, and P4 for sacrifice with cancer.

CALL SAG(S,A,G,P1,P2,P3,P4)

The following steps generate the numbers through the generation of uniform random numbers by IMSL subroutines.

U(1)=P1(1)+P2(2)
DO 5 I=2,130
U(I)=U(I-1)+P1(I)+P2(I)
5 CONTINUE
DO 16 I=1,130
E1(I)=0
E2(I)=0
16 CONTINUE
E3=0
E4=0
U(0)=0.0
DO 10 K=1,50
CALL UMACH(2,NOUT)
CALL RNSET(ISEED)
CALL DRNUN(1,R)
CALL RNGET(ISEED)
DO 6 I=1,130
IF (R.GE.U(I-1).AND.R.LT.(U(I-1)+P1(I))) THEN
E1(I)=E1(I)+1
END IF
IF (R.GE.U(I-1)+P1(I)).AND.R.LT.U(I)) THEN
E2(I)=E2(I)+1
END IF
6 CONTINUE
IF (R.GE.U(130)).AND.R.LT.U(130)+P3) THEN
E3=E3+1
ELSE
E4=E4+1
END IF
10 CONTINUE
RETURN
END

REFERENCES

1. Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 11:375–386 (1955).
2. Cochran WG. Some methods for strengthening the common χ² tests. Biometrics 10:417–451 (1954).
3. Portier CJ, Bailer AJ. Testing for increased carcinogenicity using a survival-adjusted quasial response test. Fundam Appl Toxicol 12:731–737 (1989).
4. Tan WY. Stochastic models of carcinogenesis. New York: Marcel Dekker, 1991.
5. Moolgavkar SH, Knudson AG. Mutation and cancer: a model for human carcinogenesis. J Natl Cancer Inst 66:1037–1052 (1981).
6. Thorlind T, Brown CC, Charnley G. Biologically motivated cancer risk models. Risk Anal 7:109–119 (1987).
7. Bailer AJ, Portier CJ. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. Biometrics 44:417–451 (1988).
8. Portier CJ, Hedges JC, Hoel DG. Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program’s carcinogenicity experiments. Cancer Res 46:4372–4378 (1986).
9. Tan WY, Chen CW. A nonhomogeneous stochastic model of carcinogenesis and its applications to assess risk of environmental agents. In: Mathematical population dynamics 3 (Arino
Articles • Monte Carlo results for the 3-poly test

O. Axelrod DE, Kimmel M, eds). Winnipeg, Manitoba, Canada: Wuerz Publishing, 1995.
10. Chen CW, Farland W. Incorporating cell proliferation in quantitative risk assessment: approaches, issues and uncertainties. In: Chemically induced cell proliferation: implication for risk assessment. New York: Wiley-Liss, 1991: 481–499.
11. Moolgavkar SH, Cross FT, Luebeck G. A two-mutation model for radon-induced lung tumors in rats. Radiat Res 121:28–37 (1990).

Resource Recovery Conferences 1996

Rail haul 96
Waste by Rail Conference
October 15-16 1996
Washington, DC

Transporting waste and recyclables by rail has been a reality for a decade, a concept with great potential but few success stories. Now that's changing. New projects are coming on line, and the pioneers have data to discuss and personal experiences to share. Join this unique gathering of railroad industry officials and solid waste professionals to address mutual opportunities, debate challenging issues, and explore the real world “how and why” of railhaul.

ASH - 9
MSW ASH Management
November 12-13, 1996
Washington, DC

For the 9th consecutive year, ASH management professionals from around the world will meet to learn about the latest developments in MSW ash handling, treatment, and reuse. Experts will discuss innovative technologies and strategies for ASH Management in an evolving regulatory environment. Meet with colleagues from Solid Waste and Public Works Departments, plant operators, equipment manufacturers & distributors, policy makers, and innovators ready to describe their ASH processing and management successes.

Richard Will, The Coordinate Group, Inc.
Box 3356, Warrenton, VA 22186-1956
(800)627-8913 • (540)347-4500 • FAX (540)349-4540 • email: rwill@mnscnc.com
Sponsored by Resource Recovery Report

TABLETOP EXHIBITS AT BOTH CONFERENCES