QUANTAL HEALTH EFFECTS OF THREE TOXIC AGENTS COMBINED

Abstract -- Quantal health effects such as cancer, correlated with the combined action of three toxic agents, are considered. Data on the combined effects of two agents are scarce and no such data exist for three toxicants, yet concerns have arisen about simultaneous exposure of radiation workers to three different agents. Using models developed from the analysis of health effects involving two toxicants, equations for the combined effects of three agents are derived from a more general formalism. An application of practical interest is the incidence of cancer of the esophagus and its correlation with concurrent exposures to alcohol, tobacco, and either low- or high-LET radiation.

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In recent years, the development of models for quantal health effects such as cancer has focused increasingly on the description of combined insults. Although this is the way in which exposures occur in real life, the corresponding epidemiological data are beset with many confounding or hard-to-control variables. Similarly, data from animal experiments are difficult and costly to obtain in sufficient quantity and quality. At the present time, therefore, there is little useful experimental and theoretical information available on the combined effects of two toxicants, and none for the combination of more than two agents. It is necessary, then, to put more effort into developing plausible theoretical models that encompass what is known at the present time about the effects of multiple agents, particularly about their interactions.

A practical example, for which a reasonable data base for man is available, is cancer of the esophagus, known to be caused independently by exposure to alcohol and tobacco residue, and also by nuclear radiations.[1-3] In simultaneous exposures, the incidence is enhanced by an interaction between the effects of these agents.[1,2] The marginal risk function, that is, the risk for the action of a single agent, and the nature of the interaction between alcohol and tobacco consumption are known,[1,2] but the risk function for all three agents has yet to be constructed.

The purposes of this paper are to describe a formalism for quantal health effects such as cancer that are caused by the combined action of three toxic agents, and to discuss models of interaction between the effects of these agents.

COMBINED EFFECTS OF THREE TOXIC AGENTS

In the preceding paper (this report, pp. 502-509), general formulae are derived for two models of interaction between the effects of several toxic agents resulting in the same quantal health effect. These formulae are used here to derive and discuss combined effects of three toxicants.

Independent Action Model

A model that assumes independent action for all toxic agents involved is an important yardstick for the evaluation of interactions. In the absolute risk formulation, the risk for independent action is given by

$$r = a_0 + a_1 D_1^{m_1} + a_2 D_2^{m_2} + a_3 D_3^{m_3} - \{Q\} \; ; \qquad (1)$$

Q is the overlap between the first four terms, as defined in the previous paper; a_0 stands for the background risk of the health effect; the a_i are the risk coefficients for the toxic agents i; the D_i are the doses accumulated; and, the quantities m_i are the exponents of the dominant terms in the dose-effect relationship for each agent.

In the relative risk formulation, the risk is

$$r = a_0 \left[1 + b_1 D_1^{m_1} + b_2 D_2^{m_2} + b_3 D_3^{m_3} - \{\frac{Q}{a_0}\}\right] , \tag{2}$$

where the coefficients b_i are defined by $b_i \equiv a_i/a_0$.

In many practical applications, the overlap Q is very small and can be neglected. Equations 1 and 2 are then just the sums of the marginal excess risks. Called 'additivity', this property is an often used criterion for independent action. For small risks, this usage is approximately correct, for sizeable marginal risks it is not, and Q must be calculated.

Separable Action Model

In the few cases for which the algebraic form of the interaction between two toxic agents has been determined, the mathematical properties were those of a separable function,[1,2,4] that is, in each case, the relative risk function was separable into multiplicative factors that depend on only one toxic agent. The simplest possible form of these factors is the relative marginal risk for agent i, that is, the enhancement factor for the background risk due to that agent.

With the overlap assumed to be negligibly small, the risk is then

$$r = a_0 \left[1 + b_1 D_1^{m_1}\right] \left[1 + b_2 D_2^{m_2}\right] \left[1 + b_3 D_3^{m_3}\right] . \tag{3}$$

Note that Equation 3 contains only one factor a_0, so that the model does not imply that the total risk is a product of the marginal risks, rather it implies that the total relative risk or total enhancement factor is the product of the relative risks.

ESOPHAGEAL CANCER DATA

General Information

In the U.S., cancer of the esophagus has an incidence rate of 3.10^{-5} per year. This incidence correlates with alcohol and tobacco consumption and with exposure to low-LET radiation.[1-3] In epidemiological studies, a synergistic interaction between the effects of alcohol and tobacco residue has been demonstrated.[1] Synergisms were also found for similar cancers of the oral cavity and for cancer of the larynx.[3,5] No evidence for an interaction between radiation and either alcohol or tobacco residue is available at this time, although there is a synergism for cancer of the lung in smoking uranium miners.

In the periods covered by the epidemiological studies of esophageal cancer,[1,6] smoking and drinking were largely concurrent habits, so that marginal risks for alcohol and tobacco use are difficult to obtain. At present, they are best estimated from an analysis of the combined action of the two agents.

Marginal Risks for Alcohol and Tobacco Exposure

An analysis of epidemiological data on oral and esophageal cancer has shown[2] that, within statistics, the same risk function is obtained, both with regard to algebraic structure and with the numerical value of the risk coefficients. The marginal risk for lifelong tobacco use is

$$r_t = a_0 \left[1 + (0.052 \pm 0.018)\ \dot{D}_t\right] , \tag{4}$$

where $\dot{D}_t$ is the exposure rate in g of tobacco smoked per day. The marginal risk for lifelong alcohol consumption at an exposure rate of $\dot{D}_a$ in g of pure alcohol per day was found to be

$$r_a = a_0 [1 + (0.0012 \pm 0.0002) \dot{D}_a^2] . \quad (5)$$

Due to the way the data[1] are given, exposure rates $\dot{D}_i$ are used here as the primary exposure parameters instead of using the cumulative exposure $\dot{D}_i$, which would be more appropriate. As drinking and smoking are usually lifelong habits, particularly during the period considered, the consumption rates can be assumed to be more or less constant, and exposure rate and cumulative exposure are approximately equivalent exposure parameters.

Marginal Risks for Radiation Exposure

Cancer of the esophagus is one of the neoplasms found slightly, but significantly ($0.05 < p < 0.1$), in excess among the nuclear bomb survivors in Hiroshima and Nagasaki. The doses accumulated there were almost entirely due to whole-body, low-LET irradiation, mostly gamma rays. The marginal risk function was found to be[3]

$$r_n = a_0 [1 + (0.23 \pm 0.15) D_n] , \quad (6)$$

where D_n is the cumulative low-LET, whole-body dose in Sv. The uncertainty of the risk coefficient for esophageal cancer is large, leading to a considerable uncertainty in the risks calculated. The risk is assumed to be real, because an excess radiation risk is also found in spondylitics given X-ray therapy.[7]

For exposure to high-LET radiation, the risk can be estimated if the assumption is made that the quality factor found for other tissues can be used for the esophageal epithelium.

RISK OF ESOPHAGEAL CANCER

Dosimetry of High-LET Radiation in the Esophagus

Dosimetry of high-LET particles is difficult, due to the degradation of the particle energy in an extended source. For an accurate dose calculation, geometrical information on the source would be needed. This information is not typically available. In some cases, such as this one, the problem can be overcome by calculating an upper limit to the dose.

A high upper limit can be obtained by assuming that all high-LET activity is carried in the surface layer of the bolus of food or mucus descending the esophagus, and is evenly distributed over the depth equal to the range of the particles. If it is assumed that the entire bolus surface is in contact with the surface of the esophagus, then 1/4 of the particles emitted in the bolus will contact the surface tissues of the esophagus and deposit various amounts of energy there (1985-86 *Annual Report*, LMF-115, pp. 62-65). A reasonable approximation is that - on the average - half the maximum energy of the particles will be deposited in the surface layer of the esophageal tissue. This layer also is assumed to have a depth equal to the range of the particles in tissue.

The equivalent dose absorbed by the surface layer of the esophagus is then given by

$$D_n = \frac{F Q E T}{8 S d \rho} , \quad (7)$$

where

D = equivalent dose (in Sv)

F = quality factor of alphas (20)

Q = total source strength (in Bq)

E = total particle energy (5.15 MeV = $8.25 \cdot 10^{-13}$ J)

T = transit time (10 sec)

S = tissue surface (0.0141 m^2)

d = range of particles (34.5 μm)

ρ = tissue density (1040 kg m^{-3}).

For ^{239}Pu alpha particles, the equivalent dose to the esophagus per unit source strength can be calculated to be

$$\frac{D_n}{Q} = 40.8 \text{ nSv Bq}^{-1} \tag{8}$$

for Standard Man.[8] If he works N years for 40 h/wk and 52 wk/yr, and is continuously exposed to the maximum permissible concentration of ^{239}Pu, then the rate of deposition will be

$$\frac{Q}{N} = \begin{matrix} 110 \\ 2200 \end{matrix} \text{ Bq y}^{-1} \text{ for } \begin{matrix} \text{soluble } ^{239}Pu \\ \text{insoluble } ^{239}Pu \end{matrix} . \tag{9}$$

If the ^{239}Pu deposited is removed quantitatively, by way of the mucociliary escalator and the G.I. tract, the dose rate to the esophagus will be

$$\frac{D_n}{N} = \begin{matrix} 4.4 \\ 88 \end{matrix} \text{ μSv y}^{-1} \text{ for } \begin{matrix} \text{soluble } ^{239}Pu \\ \text{insoluble } ^{239}Pu \end{matrix} . \tag{10}$$

Twenty years of occupational exposure would thus result in an equivalent dose to the esophagus of 0.09 and 1.76 mSv, respectively, and a relative radiation risk of

$$\frac{r_n}{a_0} = \begin{matrix} 1 + (2.0 \pm 1.3)\ 10^{-5} \\ 1 + (4.0 \pm 2.6)\ 10^{-4} \end{matrix} \text{ for } \begin{matrix} \text{soluble } ^{239}Pu \\ \text{insoluble } ^{239}Pu \end{matrix} . \tag{11}$$

Compared to the risks due to alcohol and tobacco consumption, this risk is negligibly small, even though it is a high upper limit.

Independent Action and Separable Interaction Risks

The independent action model for the three agents is given by

$$r_{ind} = a_0 [1 + 0.052 \dot{D}_t + 0.0012 \dot{D}_a^2 + 0.23 D_n] , \tag{12}$$

with doses and dose rates, as defined earlier. The total risk function r_{sep} for a separable interaction is given by the expression

$$r_{sep} = a_0 (1 + 0.052 \dot{D}_t) (1 + 0.0012 \dot{D}_a^2) (1 + 0.23 D_n) . \tag{13}$$

This risk is expected to lie considerably higher than predicted by the independent action model.

A Practical Example

As a practical example, assume that an individual has been working for 20 yr in a radiation environment involving ^{239}Pu and low-LET radiation. There are no elevated ^{239}Pu levels in the body, but the low-LET dose to the esophagus is estimated to be 12 ± 3 cGy. The individual is a "two-packs-a-day" smoker, putting the exposure rate $\dot{D}_t$ at 40 ± 4 g/day, and his consumption rate for alcohol is $\dot{D}_a$ = 50 ± 6 g/day.

Thus the marginal relative risk for the tobacco consumption is R_t = 3.1 ± 0.8 and the relative alcohol risk is R_a = 4.0 ± 0.9. The relative risk for the combination of exposures is R = 12 ± 4. Whereas the risk for high-LET radiation due to continuous occupational inhalation of ^{239}Pu at 1 MPC is negligible, the risk due to low-LET radiation from external sources may be just significant. At R_n = 1.028 ± 0.021, it is still marginally compatible with 1; an upper limit with a confidence level near 95% would be R_n = 1.07.

With these values, the combined relative risk for independent action of all three agents is R_{ind} = 6 ± 1, and the separable interaction risk is R_{sep} = 13 ± 4. Even with the use of the upper limit of R_n, however, neither of the two values is influenced appreciably by the radiation exposure.

DISCUSSION

Models for quantal health effects caused by exposure to three toxic agents have been constructed using different assumptions for the interaction. The independent action model provides the basis for determining whether interactions are present, whereas the separable interaction model provides a yardstick for the size of synergistic interactions. For both models, the formulae for the risk of three agents are given and discussed briefly.

As a practical example, cancer of the esophagus in correlation with the consumption of alcohol and tobacco, and with exposure to nuclear radiation, was treated in some detail. It was shown by an upper limit calculation that the dosimetry of the esophagus normally precludes large, high-LET doses from materials passing through. Unless relatively large, low-LET exposures from external sources can be demonstrated, it is thus difficult to arrive at a sizeable marginal radiation risk. The total risk is predominantly driven by the large interaction between the alcohol and tobacco exposures.

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