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# MODELING LUNG CANCER RISKS IN LABORATORY DOGS EXPOSED TO INHALED PLUTONIUM

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# MODELING LUNG CANCER RISKS IN LABORATORY DOGS EXPOSED TO INHALED PLUTONIUM

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The analyses I'll be presenting today are based on data from a lifespan study of beagle dogs exposed to inhaled plutonium being conducted at Pacific Northwest Laboratory. An important goal of this study is to increase understanding of health risks resulting from this exposure, with particular attention to lung cancer risks. Data on humans exposed to plutonium are inadequate for achieving this goal.

This slide (#1) shows the design of the experiment. Eighteen-month-old beagle dogs were exposed through inhalation to six different levels and three different types of plutonium. The lowest level corresponds to the maximum permissible dose for a plutonium worker, while the highest level is a dose at which radiation pneumonitis is likely to cause early death in many animals. $^{239}PuO_2$ was chosen because it is the form of plutonium to which people working in nuclear fuel processing and storage industries are likely to be exposed. The other forms were chosen because they result in different spatial and temporal distribution of radiation dose, and thus can provide information on the influence of these factors on risk. The analyses I'll be presenting today use only the data from the $^{239}PuO_2$ and $^{238}PuO_2$ exposed animals. All dogs in these groups are dead.

The analyses that I'll be presenting today address lung tumor risks in these animals. The analyses are aimed at quantifying these risks, examining the shape of the dose-response curve and the pattern of risk over time, and understanding differences in risks from the two exposures.

In choosing methods for analyzing these data, an important consideration is that results be in a form that can be readily compared with results of analyses of relevant human epidemiologic data. Although no adequate data are available on humans exposed to plutonium, data on humans exposed to other forms of radiation are available, and include, for example, the Japanese A-bomb survivor data and data from several studies of miners exposed to radon and radon progeny.

Analyses of human epidemiologic data have generally modeled the hazard, or age-specific risk, as a function of dose and other factors. (Slide #2) The model that has been most commonly used is a relative risk regression model in which the hazard is a linear-quadratic function of risk, and in which the

baseline risk has been handled non-parametrically by introducing separate coefficients for each age group, or, more generally, for each stratum. For analyses of the beagle dog data, we've used a similar model, but have substituted a Weibull function for the separate baseline coefficients. This substitution was made primarily because baseline risks in dogs are more uncertain than in humans; we don't have the large number of subjects with minimal exposure that are usually available in human epidemiologic studies. For this reason, it's often desirable to present risks in absolute rather than in relative terms, and the model I've indicated allows this.

With appropriate parametrization and scaling of age, the risk coefficient $\beta$ can be roughly interpreted as a lifetime risk, or more specifically as the cumulative hazard to 14 years of age (the average lifespan of control animals) for a dose received at 18 months of age. In these experiments, the inhaled plutonium delivers its dose to the lung over time, and dose needs to be treated as a time dependent variable in analyses of these data.

I'll first show results based on the dogs exposed to $Pu^{239}O_2$. This slide (#3) shows results of fitting linear, linear-quadratic, and quadratic models. It can be seen that the linear model did not fit the data as evidenced by the improvement in fit brought about by adding the quadratic term. It can also be seen that the improvement brought about by including a linear term, over fitting a pure quadratic model, was negligible. In addition to the models indicated here, a model in which the power of dose was estimated was fit; the estimated power was very close to two. Other tests for goodness of fit verified that a pure quadratic model based on the Weibull function provided a reasonable fit to these data.

Before proceeding further, I'd like to comment on dose estimation in these studies. The cumulative dose at any point in time is determined both by the amount of material inhaled and rate at which material is cleared from the lung over time. Dose estimation for these studies is complex. The initial lung burdens are estimated from external thorax counts taken near the beginning of the study. Clearance rates are estimated using both the initial counts and the amount of material found in the lung after death. In some cases, excreta data and data from sacrifice animals were also considered. This slide (#4) shows the general formula that is used to calculate dose to the lung at any time post-exposure.

In the analyses that I just presented, the initial lung burden was obtained as the external thorax count, the weight of the lung was estimated as a constant fraction of the weight of the animal, and a common clearance curve was estimated for all animals. There are several possible modifications of this procedure. One way to evaluate different dose estimation strategies is to compare how well doses calculated by different methods predict lung cancer risks. My next few slides illustrate such an evaluation.

Specifically, I've considered a modification in which the average weight of all animals is substituted for the weight of individual animals. This slide shows results of fitting quadratic models based on individual weights, and on average weights (#5). It is seen that the addition of average weight (in the second analysis on the slide) significantly improves the fit of the model. In fact, the estimates for the power $\rho$ of the ratio of the two weights was estimated to be almost exactly two, resulting in cancellation of the individual weights. Also, the model including both weights resulted in almost no improvement over a model with just average weight.

These analyses provide strong evidence that dose calculated by dividing by the average weight of the animals does a better job of predicting risks than dose calculated using the weight of the individual dogs. This may indicate that individual dog weights are not highly correlated with lung weight. Alternatively or additionally, it may be that the standard measure of dose, as radioactivity per unit of weight, is not as relevant in predicting risks as the total amount of activity.

Other modifications of the dose estimation procedure are being examined in a similar fashion. It is hoped that this evaluation will lead both to better dose estimates, and an improved understanding of which measures of exposure are the best predictors of risk.

I'd like to turn now to the comparison of risks in animals exposed to $^{239}PuO_2$ and to $^{238}PuO_2$. The reason for interest in this comparison is that the specific activity of $^{238}PuO_2$ is much higher than for $^{239}PuO_2$. This means that the two exposures differ in both the spacial and temporal distribution of dose. There are spacial differences because fewer particles of $^{238}PuO_2$ are required to produce a given average dose to the lung than of $^{239}PuO_2$. Thus $^{239}PuO_2$ probably delivers a more uniform dose to the lung.

There are temporal differences because $^{238}PuO_2$ clears the lung more rapidly, and thus delivers its dose more quickly than does $^{239}PuO_2$. This

slide (#6) shows the way that dose is accumulated for the two exposures. You can see that the $^{238}PuO_2$ dose is accumulated earlier than the $^{239}PuO_2$ dose.

Another feature of these data is that competing risks differ for the two exposures. Bone cancer is an important competing risk for $^{238}PuO_2$, because $^{238}PuO_2$ is translocated fairly quickly from the lung to the bone. Many $^{238}PuO_2$ dogs die of bone tumors before they have a chance to develop lung tumors.

I haven't yet said anything about the context of observation of tumors. This becomes especially important in comparing risks from the two exposures. We have several kinds of information relevant to establishing the time of the tumor and the context of observation. First, animals were radiographed periodically; however, these radiographs were only taken annually, which would be comparable to about every five years in a human life, and sometimes even less frequently. Second, we have the date of death, whether a tumor was observed at death, and whether the tumor was judged by the pathologist to cause the death of the animal.

In my next slide (#7) I've indicated the status of various tumors in the two groups of dogs. You'll note that there were several tumors that were not seen on radiographs, and not judged to cause death. These were generally very small tumors that were found only at necropsy and sometimes only by conducting detailed microscopic examination of the tissue. These tumors were seen primarily in the $^{238}PuO_2$ exposed dogs; in most cases the cause of death was fairly clearly a bone tumor. The way that we treat tumors observed in various contexts is clearly important in comparing risks from the two types of exposure.

There are three possible hazards that we could consider modeling: the risk of tumor observable at necropsy, the risk of tumor observable on a radiograph, and the risk of tumor causing death of the animal. The times to tumor associated with each of these hazards will differ. Today I'll present three approaches. In the first, we included only tumors judged to cause death in the animal, with the tumor time considered to be the time of death. In the second, we included only tumors seen on radiographs, with the tumor time estimated as the average of the time of the first positive radiograph and the last negative radiograph. In the third, we included all tumors, and modeled the time to necropsy by making the fairly strong assumption that the interval between necropsy time and radiograph time was a constant, taken to be one year in the analyses I'll be presenting. Another approach, which we intend

to try in the future, is to treat tumors not seen on radiographs as incidental; this approach would involve a simultaneous modeling of the hazard based on necropsy time and the hazard based on positive radiograph.

The results of these comparison are presented in my next slide (#8). These analyses were based on a quadratic model, which was found to provide a better fit to the data than several alternative models that were examined. I'v shown the quadratic coefficients for each type of exposure, and also the likelihood ratio chi-square statistic for testing the improvement in fit brought about by fitting separate coefficients over fitting a common coefficient for both exposures. It is seen that the difference in the coefficients for the two exposures is highly significant for all three of the analyses presented, with larger risks in beagles exposed to $^{239}PuO_2$. Because many dogs died before their tumors caused death, and in some cases before the tumor could be seen on a radiograph, the risk coefficients based on all tumors are larger than those based on only tumors seen on radiographs, and these latter coefficients are in turn larger than the coefficients for tumors causing death in the animals.

Certain aspects of these analyses merit further attention. The dose estimates used were preliminary, and are being refined. It is expected that examination of the ability to predict lung tumors will play a role in the choice of the best dose estimation methods. The comparison of risks from the two exposures is strongly dependent on the estimated clearance functions; additional work is needed to determine how sensitive results are to reasonable modifications of these functions.

As noted earlier, analyses in which tumors not seen on radiographs are treated as incidental are planned. In addition, further exploration of the effect of different assumptions about l ɟ periods for both doses and the Weibull function is needed. Lag periods probably should be differentiated according to the context of observation of tumors. In the analyses presented earlier, the time to necropsy was lagged by one year, the time to positive radiograph was lagged by two years, and the time to death was lagged by three years. Limited exploration of other assumptions suggest that the data probably are not strong enough to differentiate adequately among various assumptions about lag periods.

Although further refinements are needed, the analyses presented indicate that at a given cumulative dose to the lung, $^{238}PuO_2$ is less effective in

producing lung tumors than is $^{239}PuO_2$. This result could be interpreted as indicating that cumulative dose to the lung is not an adequate predictor of lung-cancer risks, and that spatial and temporal distribution of dose are important factors to consider in determining risks. These analyses also demonstrated that the lung-tumor dose-response curve is nonlinear over the observed dose range.

Slide #1:

Lifespan Studies with Inhaled Plutonium in Beagles

| $^{239}PuO_2$ | | $^{238}PuO_2$ | | $^{239}Pu(NO3)_4$ | |
|---|---|---|---|---|---|
| Initial Deposition (nCi) | Number of Dogs | Initial Deposition (nCi) | Number of Dogs | Initial Deposition (nCi) | Number of Dogs |
| 0 | 20 | 0 | 20 | 0 | 40 |
| 3.5 | 24 | 2.3 | 20 | 2 | 20 |
| 22 | 21 | 18 | 21 | 8 | 20 |
| 79 | 20 | 77 | 22 | 56 | 20 |
| 300 | 22 | 350 | 20 | 300 | 20 |
| 1100 | 21 | 1300 | 20 | 1700 | 20 |
| 5800 | 8 | 5200 | 13 | 5400 | 5 |

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Slide #2:

- Analyses of human epidemiologic data have modeled age-specific risks (hazard) as a function of cumulative exposure and other factors
- Linear-quadratic relative risk model has played important role

$$h(a, D_a) = \lambda_a (1 + B_1 D_a + B_2 D_a^2)$$

where a is age, $\lambda_a$ is the baseline risk at age a,
$D_a$ is the cumulative dose at age a, and
h is the hazard, or age-specific risk.

- Analyses of dogs are based on a Weibull model

$$h(a, D_a) = (\alpha+1)\, a^{\alpha} (\theta + \beta_1 D_a + \beta_2 D_a^2)$$

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Slide #3:

Dose-response modeling for beagles exposed to $^{239}PuO_2$

$$h(a, D_a) = (\alpha+1)\, a^{\alpha} (\theta + \beta_1 D_a + \beta_2 D_a^2)$$

| | $\alpha$ | $\beta_1$ | $\beta_2$ | Change in likelihood ratio chi-square |
|---|---|---|---|---|
| Linear model: | 1.4 | 0.35 | -- | -- |
| Linear-quadratic model: | 2.1 | 0.088 | 0.045 | +13.6 |
| Quadratic model: | 2.3 | -- | 0.059 | -1.1 |

Slide #4:

## Dose Calculation

$$D(t) = k\ I\ f(t)/w$$

where t is time post-exposture
D(t) is the dose accumulated by time t
k is a constant to provide correct units
I is the esimated initial lung burden
w is the estimated lung weight
f(t) is a function of t, obtained form the estimated clearance curve

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Slide #5:

Comparison of fits provided by the quadratic model with doses calculating by two different methods

| | Quadratic coefficient | Change in likelihood ratio chi-square |
|---|---|---|
| Dose (DI) based on weight of individual animals: | 0.055 | |
| Both doses DI and DA used: | | |
| $\beta_2\ DI^2\ (DA/DI)^{\rho}$ | 0.059, $\rho$ = 1.97 | + 4.07 |
| Dose (DA) based on average weight of all animals: | 0.059 | - 0.01 |

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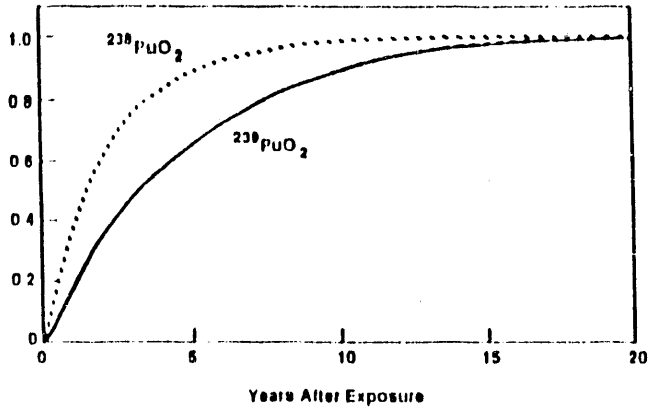
Slide #6:

Fraction of committed lung dose received by t years after exposure



Slide #7:

Context of observation of lung tumors

in beagles exposed to $^{239}PuO_2$ and $^{238}PuO_2$

| | | Positive Radiograph | No positive radiograph |
|---|---|---|---|
| $^{239}PuO_2$ | Cause of death | 41 | 6 |
| | Not cause of death | 4 | 5 |
| $^{238}PuO_2$ | Cause of death | 11 | 0 |
| | Not cause of death | 5 | 12 |

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Slide #8:

Comparison of quadratic risk coefficients

in beagles exposed to $^{239}PuO_2$ and $^{238}PuO_2$

| | $^{239}PuO_2$ | $^{238}PuO_2$ | Chi-square for improvement in fit by estimating separate coefficients |
|---|---|---|---|
| Tumors causing death only: | 0.035 | 0.0027 | 26.1 |
| Tumors seen on radiographs only: | 0.051 | 0.0038 | 44.9 |
| All tumors: | 0.066 | 0.010 | 41.3 |

# END

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