ISSUES IN THE DOSE-RESPONSE ANALYSIS OF THE MAYAK CASE-CONTROL STUDY

Dear Editors:

THE PLUTONIUM dose-response analysis of the Mayak case-control study (Tokarskaya et al. 1997) in the December 1997 issue of *Health Physics* raises a number of methodological issues that make it premature to conclude that there is a real non-linear dose-response.

An important methodological issue involves the inability of standard case-control studies to distinguish between non-linear dose-response and differences in exposure distributions across cases and controls (Robertson et al. 1994; Zhao et al. 1996).

Second, the authors maintain that they do not have to worry about the healthy worker effect, since they used workers as controls. While their method eliminates the usual problem with the healthy worker effect, the authors did not caution against trying to extrapolate any threshold found in workers to the general population. To make such an extrapolation, one needs to know how the threshold might vary across the population, particularly among the most susceptible. Risks at low doses may be dominated by a susceptible subgroup with a low threshold. Particularly, with non-linear, multi-hit models, genetically impaired individuals may already have some of the "hits" satisfied. As a result, averages over the general population may produce a different dose-response curve than averages over workers.

The most important methodological issue involves the plutonium dosimetry used in the study. Plutonium lung doses are determined from measurements of plutonium in urine, but virtually no information is given about how the conversion was made for this non-trivial exercise, other than an oblique reference to ICRP [presumably Report 54 (ICRP 1987)]. Nor is information given about when the urine measurements were made, the techniques used, their uncertainties, and how the measurement techniques changed with time. The only dosimetry-related citation is to a personal communication. The same is true of an earlier paper that describes the study population (Tokarskaya et al. 1995). Without more information about the dosimetry, it is not clear whether the non-linearity in dose-response found in this study lies in the dose conversion or in the radiation biology. There is also the possibility that the non-linearity might result from incomplete specification of the plutonium-smoking interaction.

A large number of assumptions are needed to go from plutonium in urine to absorbed lung dose. Presumably, the authors have assumed that the plutonium excretion curve is linear with total absorbed dose. The authors do not cite any studies on the linearity of the excretion curve with plutonium intake. If that curve is non-linear, there would naturally be an apparent non-linearity in their dose-response curve.

Furthermore, it appears that the authors have assumed that the excretion curve is independent of sex and smoking history. These are very risky assumptions to make in a study population that differs markedly by sex both in terms of smoking prevalence and plutonium dose. The female control population generally did not smoke and was assigned an average plutonium lung dose three times higher than the male control population (Tokarskaya et al. 1995). Unless there is some job-related reason for this discrepancy in dose between males and females, it suggests the possibility that there may be a sex-dependent or smoking-dependent excretion curve to reckon with here.

To a certain extent smoking appears to have been controlled for in the study. However, I presume that the authors used a standard interaction term that was linear in estimated dose and smoking rate. For the authors' dose response to be valid, this interaction term must control both for any smoking related differences in plutonium excretion and for the known differences in radiation risk for smokers and non-smokers (Lubin et al. 1995). We are never told to what extent the interaction terms fit the data symmetrically. If the true interaction term is more complicated than a simple product, it could lead to a false non-linearity in dose response.

As far as I can tell, the authors have not considered the possibility that the conversions of urine to dose could be sex-biased, despite an unusual situation where female controls have three times the estimated dose as male controls. Since the female cases have ten times the average estimated plutonium lung doses as the male cases (Tokarskaya et al. 1995), it appears that the high dose points on the dose response curve are for females, while the low dose points are for males. Thus, the non-linearity in dose-response conceivably could be explained by a sex-dependent excretion curve or other sex bias in the dose estimate.

It would be very interesting to see what kind of a curve the authors get by excluding the smaller number of women, and, ideally, by computing dose-response curves separately for the two sexes.

Another possible source of non-linearity in dosimetry involves a possible non-uniformity in time of plutonium intake. Unfortunately, we are not told the frequency of urine measurements nor the time period in which they began. If the measurements were begun early in the program, then it is important to know if any improvement in techniques over the years revealed any systematic discrepancies in the earlier measurements. Systematic discrepancies between different time periods could lead to an apparent non-linearity in dose-response, assuming that the annual intake of plutonium was highest in the early days of the program. On the other hand, if the measurements were begun late, then any relative errors in the excretion time curves could lead to an apparent non-linearity with plutonium uptake, assuming once again that the intakes were highest during the early days of the program. Excretion curves are known to be very uncertain at long times (Leggett and Eckerman 1987).

There are additional reasons to perform an analysis for non-linear dosimetry: The authors saw no dose-response non-linearity with external radiation, and their results are inconsistent with other studies. Although the authors cite a supportive ecologic study by Cohen on radon in homes (Cohen 1993), they do not cite case-control studies on radon in homes nor in uranium miners. The most recent analysis of the uranium-miner case-control data (Lubin et al. 1997) finds "little evidence of departures from a linear excess relative risk model" even in the lowest exposure categories.

This data set is extremely important for the understanding of plutonium health effects. Without knowing more about the plutonium dosimetry, it is impossible to know whether or not the author's findings are really inconsistent with the studies of uranium miners. The authors would provide a service by providing details about the dosimetry.

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RESPONSE TO BEYEA

Dear Editors:

IN RESPONSE to the questions and the comments of J. Beyea concerning our article (Tokarskaya et al. 1997a), we supply the following explanations and additions:

The non-linear from time function presenting the relationship of the ^{239}Pu body burden and the ^{239}Pu excretion rate in the urine was used for the plutonium dosimetry. The fit of the function was verified for several tens of cases by comparing the ^{239}Pu excretion rate with postmortem estimates of the ^{239}Pu body burden. At any time this allows the estimation of ^{239}Pu burden in the organs by the urinary excretion and, accordingly, the dose rate—the integration of which by time allows estimation of the accumulated dose (Khokhrakov et al. 1994a, b).

When analyzing the available data (more than 200 cases) the dependence of the ^{239}Pu excretion rate on sex or smoking was not revealed. The sex dependence of the ^{239}Pu excretion was not related in the experimental studies.

Apparently, there is no need for a detailed study of the time period of the urinary analysis for the cases with the highest content of ^{239}Pu, which mainly caused the non-linear dose-response, because the ^{239}Pu body burden for these cases was verified on the basis of the post-mortem investigations of tissues.

The changes in the plutonium dosimetry methods over time were taken into account when calculating the doses.

Work on improving the plutonium dosimetry is now being carried out at the biophysical laboratory, and this may lead to a change of dose estimation.

The interaction or the bias due to the smoking influence are absent in our investigation when estimating ^{239}Pu dose-response because we have adjusted (standardized) each factor against the rest. The interaction of different factors (namely radiation and smoking) was investigated by us (Tokarskaya et al. 1997b). Numerous and complicated data were obtained. These cannot be used within the limits of this article. Another article is being prepared to address this.

The distinction of the ^{239}Pu body burdens for the male and the female is not connected with sex or smoking dependence but is explained by high dose inhalation for a small female group (due to work at the limited but contaminated site without special respirators). It is necessary to note that it is difficult to theoretically imagine that sex (biological) differences can cause a ten fold difference in the ^{239}Pu accumulation.

Our study also indicates that sex does not influence lung cancer incidence. Sex was investigated by us as the independent, separately taken variable in parallel with smoking and

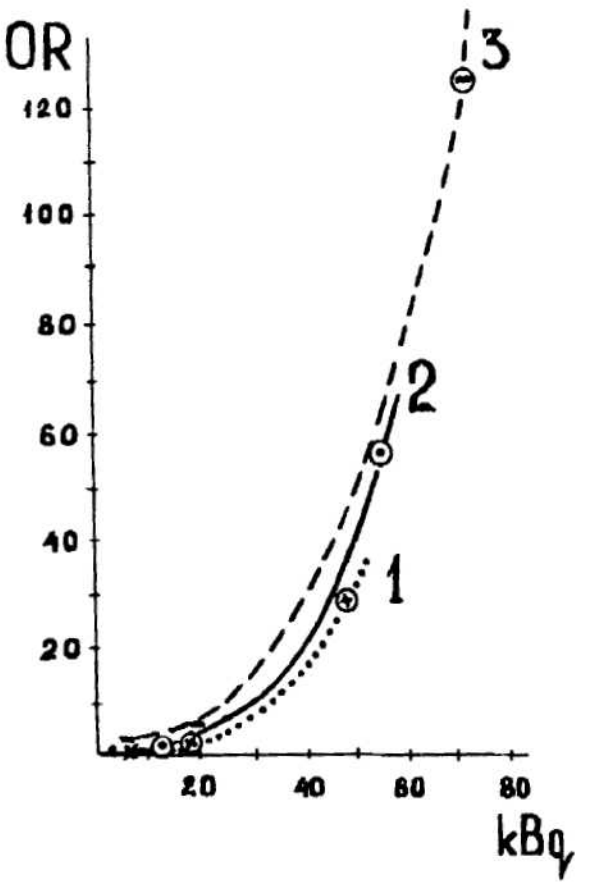

Fig. 1. Risk of lung cancer (OR-ad), depending on ^{239}Pu body burden (kBq). 1 = male, 2 = male and female, 3 = female; circles = statistically significant points.

radiation. Inclusion of sex in the regression equation was not the case. Coefficient of correlation between sex and smoking for our contingent amounts to 0.63. The literature supports that the different frequencies of lung cancer for males and females are caused not by biological factors but by the mode of life (mainly smoking). The account of smoking eliminates these distinctions (Shimizu et al. 1990).

We studied the variant with separate dose-response curves for males and females. The disposition of these curves was identical (Fig. 1). However, the statistical power of the female curve was small. Because of the small number of cases of high ^{239}Pu burden and the absence of sex distinctions for the risk of lung cancer, we used the complex group.

The separate estimation of radiation risk for smokers and non-smokers, which usually is conducted for uranium miners, is not possible in our investigation. We have a very small number of non-smokers (men); in the lung cancer group of 148 men only one did not smoke.

We did not receive any reliable points for external γ-irradiation. That is why we did not consider it possible to estimate the character of dose-response.

We can not agree with Beyea that the workers of the plutonium plant and uranium miners would have similar dose-responses. It is known that these contingents have different localization and histological types of lung tumors (plutonium-mainly adenocarcinoma, Tokarskaya et al. 1995; radon-mainly squamouse-cell cancer). This is obviously caused by different distribution of radioactivity in the lungs. Furthermore, there are differences in the other work conditions for these contingents (for example, mycotoxins in the mines). It is necessary to take into account such important factors as the very high burden of ^{239}Pu for the last subgroup of our contingent, which is just the cause of the expressed non-linearity. The ratio of excess of the admissible level of ^{239}Pu for this point is approximately 73. The ratio of excess of the admissible level of WLM radon for uranium miners having the highest exposure levels are only 30–45 (according to the data of the publications available for us). The ratio of excess of the admissible level of ^{239}Pu equal to 30–45 on our dose-response curve corresponds to the linear part of the curve.

We agree that there might be a methodological issue involving the inability of the standard case-control methods to adequately distinguish between the non-linear dose-response curve and differences in exposure distribution across the cases and the controls when the exposure variables are continuously measured. We hope to address this issue in a future study. At the present time we should note that we used not continuous but categorized variables.

In conclusion, it should be mentioned that we intend to continue our investigations and we plan to increase substantially the contingent (for account of new cases of cancer and expanding the control group), to use the dose estimates received on the basis of improved plutonium dosimetry, and to use refined statistical methods. That is why the dose-response relationships presented in our article may be considered as the preliminary ones.

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