Comments on "Protracted Radiation Exposure and Cancer Mortality in the Techa River Cohort" by Krestinina et al. (Radiat. Res. 164, 602–611, 2005)

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LETTERS TO THE EDITOR

Comments on "Protracted Radiation Exposure and Cancer Mortality in the Techa River Cohort" by Krestinina *et al.* (*Radiat. Res.* 164, 602–611, 2005)

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I read with great interest the recent article by Krestinina *et al.* (*1*), which reported the results of a cohort mortality study of the extended Techa River cohort. I was especially intrigued by the authors' conclusion that this study provided ''strong evidence of long-term carcinogenic effects of protracted low-dose-rate exposures''. If this claim were borne out, it would set this study apart from the numerous other studies of such exposures that have failed to detect carcinogenic effects. I would like to submit two observations for the authors' and readers' consideration.

First, the authors attribute the apparent increase in cancer mortality they observed solely to radiation exposure. However, it is at least possible, if not probable, that the liquid effluents discharged into the Techa River from the Mayak complex contained other nonradioactive, toxic and/or carcinogenic chemical components. If so, this would present a very real potential for confounding the results of this study. This possibility should be explored and discussed before attributing the putative increase in mortality to radiation exposure alone.

But there is an even more serious issue: the absence of a quantitative analysis of uncertainty. In particular, while the authors caution that there are large uncertainties in the dose estimates, they refer the reader to a paper by Napier *et al.* (*2*) for details. The authors' warning seems, if anything, understated, since Napier *et al.* report ranges of uncertainty of about a factor of four to five for external doses and ranges for internal doses, reported as ratios of the 97.5th percentile to the 2.5th percentile, as a factor of 20–30 for the TRDS-2000 dosimetry system used in this study. The authors did not display error bars on the data points for either the ERR or the dose axes in Figs. 1 and 2 and did not offer quantitative details on the magnitude of the uncertainties in the text; therefore, the reader is left to assume that the uncertainties in the current paper are as large as those reported by Napier *et al.* If so, these uncertainties combined with the other limitations the authors acknowledge in their paper make the conclusion that the results of this study ''provide clear evidence of elevated solid cancer and leukemia mortality risks and a strong dose–response relationship associated with exposure to radiation from the contaminated Techa River'' seem far more definitive than the data warrant.

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2. B. A. Napier, N. B. Shagina, M. O. Degteva, E. I. Tolstykh, M. I. Vorobiova and L. R. Anspaugh, Preliminary uncertainty analysis for the doses estimated using the Techa River dosimetry system—2000. *Health Phys.* **81**, 395–405 (2001).

[1] The findings and conclusions presented have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

Reply to Comments on "Protracted Radiation Exposure and Cancer Mortality in the Techa River Cohort" by Krestinina *et al.*

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We appreciate Dr. Ulsh's interest in our paper and understand his concerns about uncertainties in the risk estimates. While we are well aware of the many uncertainties associated with both the nature of the exposures received by Techa River residents and the large uncertainties in individual dose estimates, we think that this study does provide ''strong evidence of long-term carcinogenic effects of protracted low-dose radiation exposures''. We welcome the opportunity to address the issues raised in Dr. Ulsh's letter.

There is no doubt that a variety of chemicals were released into the Techa River as a result of Mayak operations. A 1951 report from the Mayak archives describes the nature of the releases into the river (*1*) during the early years of Mayak operations. According to this report, the releases into the Techa River were primarily solutions of sodium nitrate and sodium acetate with small amounts of iron hydrate and various organic substances. Qualitative analysis indicated the occurrence of traces of trivalent chromium and manganese residues. Neither sodium nitrate, sodium acetate nor the other chemicals indicated in the Mayak report are included in the current IARC list of known or suspected human carcinogens (groups 1, 2A and 2B in http://monographs.iarc.fr/ENG/Classification/index.php). Furthermore, cytogenetic analyses of 47 exposed Techa River residents and 20 unexposed individuals did not reveal elevated levels of chromatid exchanges or other indicators of exposure to mutagenic chemicals (*2*).

Of course these reports do not rule out the possibility of the presence of carcinogenic compounds in the river water; thus it is useful to consider the likelihood that exposures to such compounds, if present, would induce apparent radiation dose–response functions like those seen, when in fact none are present. For this to be the case, it would be necessary for the exposure to be related to both dose and disease outcome; i.e., the magnitude of the exposure to carcinogenic chemicals would have to be highly correlated with the soft tissue radiation dose estimates used in our solid cancer analyses and the bone marrow doses used in the leukemia analyses and for the mixture of chemical exposures to increase rates for leukemia and a broad spectrum of solid cancers. In our view, these conditions are not likely. Because of the nature of the radiation exposures, the soft tissue and bone marrow doses for the Techa River cohort members are not highly correlated; thus it is difficult to see how chemical exposures could explain both the solid cancer and leukemia radiation dose responses. It also seems unlikely that the dynamics of the transport of carcinogenic chemicals down the river would mimic that of the mixture of radionuclides that resulted in the radiation exposures. Furthermore, there are few chemicals known to cause both leukemia and a wide variety of solid cancers.

In addition to the chemicals released by Mayak, there was contami-

nation of the river water from the use of pesticides and other agricultural chemicals by the farms along the river. Less is known about these contaminants than about the Mayak releases, but arguments similar to those described above for the Mayak chemical releases should pertain.

Dr. Ulsh also raises the issue of the effect of dosimetric uncertainties on inference about radiation effects on cancer risks in the Techa River cohort. As discussed by Napier *et al.* (*3*), there are considerable uncertainties in the dose estimates for individual cohort members. These uncertainties arise for a variety of reasons, including uncertainties about the precise nature of the releases into the river, the parameters used in dose computation models, and the fact that the current dosimetry system individualizes doses using individual residence history information based on the assumption that all residents of a given village in a given year lived in a single location (corresponding to the location of the typical residence in that village) and had common dietary habits. In general, errors in assumptions about the nature of the source term or other aspects of the underlying dosimetry models would tend to rescale doses in a fairly consistent manner for all cohort members. Although such changes could alter risk estimates, we do not think that such uncertainties would change our conclusion that there is strong evidence of radiation effects in this cohort. As mentioned previously, considerable uncertainty in individual dose estimates occurs as a result of the use of representative village-specific residence and dietary patterns. This leads to grouping or ''Berkson'' errors in the individual dose estimates, such that the variability in the true doses is greater than that in the estimated doses, but if the doses assigned for each group (village) are equal to the mean for that village, then this type of error will result in little, if any, bias in the dose–response estimates. The effect of errors, uncertainties and incompleteness in individual information used in dose estimation is most likely to lead to a downward bias in risk estimates and reduce the power to detect an effect if it exists.

We did not and do not claim that the Techa River cohort data provide definitive quantitative estimates of the effects of protracted low-dose-rate radiation exposures. We are continuing to refine our analyses, and efforts are under way to improve the dosimetry system. The new system will include information on uncertainty that will allow for more quantitative assessments of the effects of dose estimation error on risk estimates. Despite (and in some sense in spite of) the large uncertainties in individual dose estimates and the possibility that non-radiation exposures may have had some impact on cancer rates in this cohort, we think the data provide compelling evidence of radiation effects on cancer risks among Techa River residents but that the point estimates of the risks are imprecise.

Finally, we think Dr. Ulsh's statement that ''If this claim were borne out, it would set this study apart from the numerous other studies of such exposures which have failed to detect carcinogenic effects'' does not fully summarize current epidemiological data. While it is not clear what Dr. Ulsh means by ''such exposures'', we can just mention that the largest study of nuclear workers (*4*) reported a significant dose response for solid cancers (ERR per Sv 0.97, 95% CI 0.14, 1.97) that is very similar to the results from the Techa River ERR per (Gy 0.92, 95% CI 0.2; 1.7). While the ERR for leukemia excluding chronic lymphocytic is considerably higher in the Techa River study (6.5, 95% CI 1.8; 24) than in the nuclear worker study (ERR per Sv 1.93, 95% CI $<$ 0 to 8.47), the confidence intervals still overlap. And as we mentioned in the paper, the atomic bomb survivor risk estimates are included in the 95% confidence intervals for the ETRC estimates. If uncertainties in ETRC dose estimates are taken into account, the confidence intervals for the ETRC risk estimates will be even wider. Thus the current data do not indicate that the cancer mortality risks differ significantly in the two populations.

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