Chromosome Aberrations in a Group of People Exposed to Radioactive Releases from the Three Mile Island Nuclear Accident and Inferences for Radiation Effects

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Chromosome aberrations in a group of people exposed to radioactive releases from the Three Mile Island nuclear accident and inferences for radiation effects

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Abstract

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Recently, it has been proposed that the doses received from ^{133}Xe released during the accident in 1979 at the Three Mile Island (TMI) plant in Pennsylvania were much higher than has been conventionally assessed because of a gross underestimation of the relative biological effectiveness of electrons from beta-particle-emitting radionuclides within the body. The central evidence cited in support of this proposal was the doses derived from cytogenetic analyses of blood sampled in the mid-1990s from people living near TMI at the time of the accident. However, the chromosome aberration data show a marked discrepancy in biodosimetric estimates evaluated from the frequencies of stable translocations and unstable dicentrics (corrected for temporal attenuation), strongly suggesting that exposures to clastogenic agents occurred long after the TMI accident. Few details have been reported on the people providing the blood samples and how they were selected for study. Crucially, this lack of information includes the distributions in the exposed and control groups of age at sampling, which is a critical factor in interpreting translocation data. Contrary to the recent claim, these cytogenetic data offer no support to the suggestion of a serious underestimation of internal doses from beta particles or from ^{133}Xe discharged during the TMI accident.

Introduction

Following the accident in March 1979 at the Three Mile Island (TMI) nuclear power plant near Harrisburg, PA, (*1-3*) there have been a number of assessments of radiation doses and health effects in the nearby population (*4-8*). The broad consensus has been that population doses were very small, with individual absorbed doses of, at most, a few mGy and a collective committed effective dose of around 40 person Sv (*2*). As a consequence, it seems highly unlikely that radioactive releases during the accident causally relate to observed variations in cancer rates near the TMI plant (*4-7*). However, one study has suggested otherwise (*9*), but this has remained controversial (*10-15*).

Recently, Datesman (*16*) has argued for a substantial re-evaluation of the internal doses received from intakes of beta-particle-emitting radionuclides released during the TMI accident. In support of this proposal he cites the results of a biodosimetry evaluation for persons living in the vicinity of TMI at the time of the accident (*17*). This assessment implied much higher doses, perhaps approaching 1 Gy, may have resulted from the radioactive releases; the TMI accident released to atmosphere about 370 PBq of noble gases, mainly ^{133}Xe, and some 0.55 PBq of ^{131}I (*2*). Datesman (*16*) has argued that this large discrepancy with previous dose estimates is due to a fundamental and severe underestimation of the relative biological effectiveness (RBE) of beta particles emitted by radionuclides within the body, which he suggests is due to the phenomenon of "shot noise" that has been neglected in conventional dose assessments (*18, 19*); as a consequence, the impact on health of the release of ^{133}Xe during the TMI accident has also been grossly underestimated (*16*). The proposed radical re-evaluation of tissue doses received from internally emitted electrons has significant ramifications beyond just TMI emissions, such as the

use of ^{133}Xe as a radiopharmaceutical and the health impact of intakes of other beta-particle-emitting radionuclides.

The purpose of this review is to examine the inferences that may be drawn from the results of the biodosimetry of blood samples taken from persons exposed to radiation following the TMI accident, as reported by Shevchenko *et al.* (*20*), and the light this casts on the support that Datesman claims these results provide for his hypothesis (*16*).

Chromosome aberration data

The key evidence cited by Datesman (*16*) was the cytogenetic analysis by Shevchenko and Snigiryova (*17, 20, 21*) of peripheral blood lymphocytes (PBL) sampled from people living near the TMI plant. Shevchenko and Snigiryova (*20*) reported that, based on the frequency of stable chromosome translocations measured in these PBL samples together with an appropriate dose-response curve relating translocation frequency to gamma dose, a dose of 0.3 Gy was obtained. They noted that this dose estimate assumed an acute exposure, so to account for chronic exposure following the TMI releases they adjusted this dose upwards by a factor of 2-3 to produce their final dose estimate of 0.6-0.9 Gy.

Ionizing radiation is a well-known carcinogen in humans (*22, 23*), and is also a known clastogen, exposure to which will result in chromosome breakage and rearrangement, and more weakly, point mutations. Indeed, chromosomal aberrations are a reliable marker of radiation exposure (*24*) (although they also measure exposure to chemicals such as benzene and various chemotherapeutic agents) and can represent an early biological predictor of cancer risk (*25, 26*). Traditionally, radiation biodosimetry has relied on the frequency of dicentric chromosome aberrations in PBL (*27*). Dicentrics are easily identifiable using conventional staining and are a remarkably sensitive indicator of exposure because of their low background frequency; some

laboratories incorporate centric rings into their analyses but because it is generally believed that they occur rarely, their inclusion makes little practical difference (*28*). However, as discussed below, dicentrics and centric rings are unstable and their frequency in PBL decreases with increasing time since exposure. Translocations are stable aberrations that persist through cell division and their presence in PBL is maintained because descendants of irradiated bone marrow stem cells carrying translocations survive and appear in the peripheral blood. A long time after exposure the translocation prevalence is a measure of the average dose to the active bone marrow because then the PBL that are scored are the descendants of the stem cells originally irradiated, while for shorter times since exposure the translocations will result from both damage to stem cell precursors and direct damage in long-lived lymphocytes. Owing to the temporal stability of translocations, for the assessment of historical exposure the translocation is the chromosome aberration of choice (*27*).

In 1994-1995, Shevchenko and Snigiryova (*20*) obtained PBL samples from 29 people assumed to be exposed to radionuclides released during the TMI accident:

> "The basis for such an assumption were the signs of radiation damages in people (skin reddening, peculiar metallic smack in the mouth, irritation of mucous membranes, vestigo, vomiting, diarrhea, etc.) at the time of the accident and also a number of diseases that occurred some time later [*sic*]." (*20*).

PBL samples from a subgroup of 6 of these 29 people were analysed for translocations using fluorescence *in situ* hybridization (FISH). Apart from the age range of 25-75 years, no details of the group of 29 people were presented by Shevchenko and Snigiryova (*20*), so that the distributions of persons by age group, sex, smoking status, location at the time of the releases from the TMI accident, and other relevant information were not provided. Nor were details provided of how the

subgroup of 6 persons were selected from the full group of 29 persons, and no distribution data were reported for the subgroup, including the age range. As discussed further below, a particularly important omission is the distribution of age at PBL sampling, because the frequency of translocations increases with attained age.

A group of 12 healthy middle-aged men from Moscow had provided PBL samples as controls for a previous study of translocations in Chernobyl "liquidators" (emergency and clean-up workers), and also for a study of people from the Altai region of Russia (in relation to exposure to radioactive fallout from the Semipalatinsk nuclear weapons testing site in present-day Kazakhstan), and these 12 men were also used as a control group in the TMI study. It would appear that the TMI exposed group was selected, presumably from among those living near the TMI plant, on the basis of some degree of ill health (see above), but the controls were healthy Russian men, so the experimental design of the study is therefore somewhat compromised.

The lack of detailed medical histories in the reports of Shevchenko and Snigiryeva (*17, 21, 29*) is troubling, particularly because of the implication that at least some of the members of the TMI exposed group were suffering various health conditions (see above). In general, it is strongly recommended that dose estimates based on assessed translocation yields should not be made in the absence of sufficient information on recent medical or other radiation exposures, or where applicable, radiomimetic (DNA double strand break (DSB) inducing) chemical exposure information (*30*).

Shevchenko *et al* (*17, 21, 29*) found stable translocations in the TMI exposed subgroup of 6 persons at a prevalence of 15.5 (95% confidence interval (CI): 9.0, 24.8) x 10^{-3} per genome equivalent, 5.1 (95% CI: 2.3, 11.5) times greater than that in the control group of 12 male Muscovites, of 3.2 (95% CI: 1.7, 5.5) x 10^{-3} per genome equivalent (Table 1); here and elsewhere

we compute confidence intervals (CI) by use of the exact Poisson CI based on the reported numbers of aberrations (*31*). Assuming that these two groups are directly comparable with respect to their background translocation frequencies, this difference implies, using the linear dose-response coefficients from Edwards *et al* (*28*) for ^{137}Cs or ^{60}Co gamma rays of 25 and 18 per 1000 cells per Gy, respectively, an estimated dose ranging from 0.49 (95% CI: 0.19, 0.79) Gy to 0.68 (95% CI: 0.26, 1.10) Gy. As recommended by Edwards *et al* (*28*) we use the calibration factors for dicentric yield, which would be expected to be similar to those for stable translocations a short time after exposure.

As we discuss in detail below, owing to the increase in frequency of translocations with attained age, it is important to take account of age at sampling in comparing translocation frequencies between exposed and control groups. However, rather disturbingly, Shevchenko and Snigiryova (*17, 21, 29*) provide no information on sampling age for the TMI subgroup of 6 people used in their translocation analysis, so we have had to assume that attained ages are similar in the exposed and control groups in estimating doses from their data; Shevchenko and Snigiryova (*17, 21, 29*) do not describe how they have adjusted for age when deriving their dose estimates.

In addition to these translocation frequencies, Shevchenko and Snigiryova (*20*) measured the frequency of dicentrics and centric rings in the full TMI exposed group of 29 persons, and in a separate control group of 82 men originally selected for a study of Chernobyl liquidators (*32*). They reported a dicentric and centric ring frequency in the TMI group of 2.0 (95% CI: 1.4, 2.9) per 1000 cells, and a control frequency in the unexposed group of 82 Russian men of 0.19 (95% CI: 0.06, 0.43) per 1000 cells (Table 1). If the cytogenetic analysis had been carried out soon after acute exposure, this difference in frequencies implies a dose of 0.07 (95% CI 0.04, 0.10) Gy or

0.10 (95% CI: 0.06, 0.14) Gy when using the linear term in the dicentric dose-response for ^{137}Cs and ^{60}Co gamma rays, respectively, as given above (*28*).

However, the more relevant estimate reported by Shevchenko and Snigiryova (*17, 21*) is from their analysis of dicentrics and centric rings in the TMI exposed subgroup of 6 persons chosen for further study; they reported aberration rates of 4.6 (95% CI: 2.5, 7.8) per 1000 cells in the exposed subgroup (Table 1). An analysis of dicentrics and centric rings in PBL from the control group of 12 men from Moscow used for the translocation analysis has not been reported, but using the frequency rate in the control group of 82 Russian men, of 0.19 (95% CI: 0.06, 0.43) per 1000 cells (*17, 21*), the difference in these aberration rates implies a dose of 0.18 (95% CI: 0.08, 0.27) Gy or 0.25 (95% CI: 0.11, 0.38) Gy using, respectively, the linear terms in the dicentric dose-response curves for ^{137}Cs and ^{60}Co gamma rays, as given above (*28*), if the analysis had been done soon after exposure.

However, the cytogenetic analysis was far from being conducted soon after exposure: Shevchenko and Snigiryova (*17*) stated that the blood samples were taken from the TMI exposed group in July-August 1994 and January-February 1995, so about 15-16 years after the accident. A recognized drawback of the dicentric assay is that the chromosome damage is unstable and cells with dicentrics are very unlikely to pass through cell division. Such cells are therefore eliminated from the peripheral blood lymphocyte pool at the rate that cell renewal occurs. Dicentrics decay fairly rapidly in PBL with an estimated average half-life of about 3 years (*27*). This implies that over 15-16 years dicentrics would be reduced by a factor $\sim(1/2)^5 = 0.03$. Consequently, the dicentric frequencies reported by Shevchenko and Snigiryova in the subgroup of 6 exposed persons selected for further study (*17, 21*) relate to an acute dose received 15-16 years earlier of about 5.7-7.9 Gy. This is markedly greater than the dose estimate of about 0.49-0.68 Gy obtained from the

analysis of translocations in PBL samples taken from the same subgroup of 6 persons. Even if the dose of about 6-7 Gy was received over a few weeks (the half-life of ^{133}Xe is 5.27 days) this would result in significant and obvious early deterministic effects, including bone marrow syndrome (the LD_{50} for which would be in the range 6.0-9.4 Gy, assuming the dose is delivered over 2 weeks), embryonic death (the LD_{50} for which, for death at 150-270 days of gestation, would be in the range 6.0-6.5 Gy, assuming the dose is delivered over 2 weeks), cataract and temporary sterility (*33*).

In deriving the dose estimates above, dose-response relationships for aberration frequencies following gamma irradiation have been applied in line with assumptions made by Shevchenko and Snigiryova in their derivation of dose estimates (*17, 29*).

Further considerations

Our analysis of the translocation data did not consider the impact of attained age on background aberration frequencies. Chromosome translocations increase quite markedly with attained age, as has been well documented in an international study (*34*). The age range of the full group of 29 TMI exposed persons was 25-75 years (*35*) (the mean age has not been reported), and although the age range of the subgroup of 6 TMI exposed persons is unpublished it cannot be wider than this. In comparison, the age range of the 12 men from Moscow who formed the control group for the translocation analysis was 39-62 years (mean age of 49 years and standard deviation of 7 years) (*20, 36*). However, the translocation rate in this control group, of 3.2 (95% CI: 1.7, 5.5) x 10^{-3} per genome equivalent (*17, 21, 29*), implies an average age of, at most, about 35 years, given the mean background translocation frequency for men in the 35-39 year age group of 6.5 (95% CI: 5.6, 7.7) x 10^{-3} per genome equivalent reported by Sigurdson *et al.* (*34*). This is a very troubling inconsistency. In this respect, in general, it is strongly recommended (*37*) that accurate dose estimates can only be made on the basis of *excess* (assumed radiation-induced) translocation rates

assessed against age-standardized expected background frequencies. That Shevchenko and Snigiryova (*17, 21*) do not provide appropriate information on the distributions of age at sampling of the various groups and subgroups is most unusual.

Stable translocations do not (unlike dicentrics) decay over time. Therefore, in order for the dose estimates from the reported levels of dicentrics and translocations in the subgroup of 6 TMI exposed persons to be compatible, it is very likely that the relevant radiation exposures in these individuals must have occurred from another source of radiation some years after TMI, indeed shortly before PBL samples were taken in 1994-1995. Alternatively, it is possible that the observed levels of chromosome aberrations are consequent on exposure to other clastogens, for example benzene or some type of chemotherapeutic drug. Indeed, Shevchenko and Snigiryova stated that:

> "In selecting a group of patients [from the TMI area], their possible diagnostic and therapeutic irradiation as well as a number of additional factors that might influence the results of cytogenetic analysis were taken into account." (*29*)

This suggests that some of the "patients" might have received radiation or other relevant exposures for medical purposes. How these other possible sources of radiation exposure and additional factors were "taken into account" by Shevchenko and Snigiryova (*29*) was not explained.

On a related point, how the subgroup of 6 persons was selected from the full TMI exposed group of 29 people has not been reported. The dicentric and centric ring frequency in the full group is 2.0 (95% CI 1.4, 2.9) per 1000 cells, while that in the subgroup is 4.6 (95% CI 2.5, 7.8) per 1000 cells. If it is assumed, as seems reasonable, that the subgroup measurements are a subset of the full set of measurements then the frequency for the remaining 23 members of the group is 1.4 (95% CI: 0.8, 2.2) per 1000 cells, significantly lower (p=0.001) than that for the subgroup of 6 persons.

This emphasises the importance of knowing how the subgroup of 6 persons was selected for the translocation analysis.

Datesman (*16*) has concluded from his theoretical modelling of the incorporation of the impact of shot noise upon the distribution of the energy dissipated in tissues by electrons emitted by radionuclides within the body that the RBE-weighted absorbed dose received from ^{133}Xe released during the TMI accident is in the range 0.82-1.7 Gy, implying a very large RBE for the electrons. If this novel and radical proposal is correct, this would have profound implications for radiological protection involving intakes of beta-emitting-radionuclides. However, the evidence for large doses received from ^{133}Xe, or indeed any significant exposure, released from TMI as derived from the cytogenetic study of Shevchenko *et al* (*17, 21, 29*) is unsubstantiated, as we have demonstrated here, and realistically, Datesman (*16*) cannot claim support for his hypothesis from these data. We are unaware of other data suggesting such a gross underestimation of doses received from internally emitted beta particles (*38, 39*).

Conclusions

In conclusion, we have highlighted some disturbing inconsistencies in the chromosome aberration data of Shevchenko *et al* (*17, 21, 29*), which cast substantial doubt on the suggestion that these data provide evidence that doses received as a consequence of the radionuclides released during the TMI accident are much higher than previously assessed. The available information suggests that the TMI "exposed" group used by Shevchenko *et al* (*17, 21, 29*) were exposed to radiation or other clastogens close to the time of blood sampling in the mid-1990s, which therefore had nothing to do with the TMI accident. In consequence, the cytogenetic study of Shevchenko *et al* (*17, 21, 29*) does not provide evidence in support of a fundamental error in the RBE of electrons from beta-particle-emitting radionuclides within the body, as proposed by Datesman (*16*).

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Table 1. Summary of the results of the chromosome aberration analyses conducted and reported by Shevchenko *et al* (*17, 21, 29*) for the Three Mile Island exposed group and subgroup, and the two control groups of Russian men. The chromosome aberration analyses are for stable translocations derived from fluorescence *in situ* hybridization (FISH) and for unstable dicentrics and centric rings derived from conventional scoring.

Groups of persons	Number of persons	FISH				Dicentrics and centric rings		
		Number of cells scored	Number of translocations	Frequency of translocations per 10^3 cells (95% CI)	Frequency of translocations per 10^3 genome equivalent (95% CI)	Number of cells scored	Number of dicentrics or centric rings	Frequency of dicentrics and centric rings per 10^3 cells (95% CI)
Exposed	29	N/A	N/A	N/A	N/A	14,854	30	2.0 (1.4, 2.9)
Exposed Subgroup	6	3468	17	4.9 (2.9, 7.8)	15.5 (9.0, 24.8)	3024	14	4.6 (2.5, 7.8)
Control 1	12	13,586	13	1.0 (0.5, 1.6)	3.2 (1.7, 5.5)	N/A	N/A	N/A
Control 2	82	N/A	N/A	N/A	N/A	26,849	5	0.2 (0.1, 0.4)

N/A, not applicable