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CURRENT USE AND FUTURE NEEDS OF BIODOSIMETRY IN STUDIES OF LONG-TERM HEALTH RISK FOLLOWING RADIATION EXPOSURE

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Abstract

Biodosimetry measurements can potentially be an important and integral part of the dosimetric methods used in long-term studies of health risk following radiation exposure. Such studies rely on accurate estimation of doses to the whole body or to specific organs of individuals in order to derive reliable estimates of cancer risk. However, dose estimates based on analytical dose reconstruction (i.e., models) or personnel monitoring measurements, e.g., film-badges, can have substantial uncertainty. Biodosimetry can potentially reduce uncertainty in health risk studies by corroboration of model-based dose estimates or by using them to assess bias in dose models. While biodosimetry has begun to play a more significant role in long-term health risk studies, its use is still generally limited in that context due to one or more factors including, inadequate limits of detection, large inter-individual variability of the signal measured, high per-sample cost, and invasiveness. Presently, the most suitable biodosimetry methods for epidemiologic studies are chromosome aberration frequencies from fluorescence *in situ* hybridization (FISH) of peripheral blood lymphocytes and electron paramagnetic resonance (EPR) measurements made on tooth enamel. Both types of measurements, however, are usually invasive and require difficult to obtain biological samples. Moreover, doses derived from these methods are not always directly relevant to the tissues of interest. To increase the value of biodosimetry to epidemiologic studies, a number of issues need to be considered including limits of detection, effects of inhomogenous exposure of the body, how to extrapolate from the tissue sampled to the tissues of interest, and how to adjust dosimetry models applied to large populations based on sparse biodosimetry measurements. The requirements of health risk studies suggest a set of characteristics that, if satisfied by new biodosimetry methods, would increase the overall usefulness of biodosimetry to determining radiation health risks.

INTRODUCTION

Biodosimetry, or the measurement of biological markers that can be quantitatively related to the magnitude of the radiation dose received, can conceivably play an important role in long-term studies of radiation health risk. It is our goal here to discuss the value of biodosimetry in that context and how it might be utilized to a greater potential. The value of biodosimetry measurements to health risk studies is primarily due to their potential to provide cumulative measures of radiation dose to study subjects independent of model-based estimates. Those measurements which, if dependable, can be used to corroborate or contradict doses assigned to individuals from other sources of data or estimation techniques including all types of exposure assessment models (Kleinerman 2006, Simon et al. 2007). It is important to

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understand that biodosimetry does not include the measurement of radiation whether it be in the environment or emitted from radioactivity internal in study subjects, but it is limited to the evaluation of biological markers of the dose received (ICRU 2002).

The availability and requirements for biodosimetric techniques used at long times after exposure, i.e., from 6 months to more than 50 years, are unique compared to the requirements for methods used for immediate dose estimation. These qualities were discussed in detail in Simon et al (2007). In addition to the fundamental requirement that the assay measures a physical or biological change that is proportional to the energy absorbed, the signal must be highly stable over time and specific to the type of radiation (e.g., ionizing vs. non-ionizing) to enable reasonably precise determination of the absorbed dose decades after the exposure was received.

High cost and invasiveness have for the most part prohibited conducting biodosimetry measurements on a large enough scale to replace analytical dose reconstruction in epidemiologic investigations. Despite those limitations, however, there has been substantial use of two biodosimetric techniques in studies of irradiated populations: fluorescence *in situ* hybridization (FISH) of peripheral blood lymphocytes and electron paramagnetic resonance (EPR) measurements made on tooth enamel. In many of the applications of these methods, the intent has been to identify highly exposed persons or confirm suspected exposures, or determine an external dose representative of persons residing or working in a specific location. Most of these investigations have had to assume uniformity of whole-body exposure as a simplistic assumption. Moreover, most estimates have pertained to external exposure with only a few intended to estimate internal dose.

There is much interest today in biodosimetry techniques that would be useful immediately after mass exposure events (Alexander et al. 2007). However, there is also a need for improved biodosimetric techniques to assist in long-term epidemiologic investigations so that radiation cancer risks can be estimated as well as possible. The latter subject is the focus of this paper.

DISCUSSION

The use of biodosimetry measurements in long-term health risk studies is presently limited though it could potentially be increased if more capable and suitable techniques can be developed. There are several requirements for biodosimetry measurements that must be met to make them useful to health risk studies. In this paper, we emphasize these requirements: the need to retrospectively estimate organ doses at long times after exposure with reasonably good precision, with little bias, with low invasiveness, and with low to moderate cost. The following sections discuss the basic concepts of health risk studies, the possible role of biodosimetry in health risk studies, and desired characteristics of new measurement techniques for incorporation into future health risk studies.

What are long term health risk studies?

Long-term health risk studies of radiation exposure, also known as radiation epidemiology studies, attempt to determine the association between radiation exposure and a health outcome, usually cancer, which occur over a specified period of time following exposure – a minimum of about two years for leukemia and about 10 years or more for solid cancers. Studies of radiation-related cancer explore possible causal relationships of radiation with specific cancer types by establishing a dose-response relationship. Typical dose-response relationships demonstrate that the risk of cancer induction increases with increasing radiation dose. Examples of well-established dose-response relationships include the risk of solid cancers (Preston et al. 2007) and malignant and benign thyroid disease in the atomic-bomb survivors (Imaizuimi et al., 1995).

Other questions that long-term health risks studies seek to answer include:

- Is there evidence that radiation exposure is the cause, or one several causal factors, for the development of a particular cancer type in excess of its natural rate of occurrence?

- What is the time-course of radiation-related cases of disease?

- What is the relationship between disease occurrence and (i) total dose, (ii) dose rate (acute or chronic), (iii) type of radiation, (iv) LET of radiation, (v) age at exposure,(vi) attained age or age at appearance of disease and (vii) gender?

Health risk studies should consider whether there are any confounding factors[‡] or biases in the study design or methodology that could explain any apparent associations that may be found between radiation exposure and cancer. If necessary, studies should take into account how the radiation risk is modified by other factors such as age, gender, time since exposure to disease occurrence, genetic susceptibility, and exposure to other environmental carcinogens such as tobacco smoke.

Epidemiologists use various analytic study designs to evaluate the risk of radiation-related cancer, primarily the cohort or follow-up design and the case-control design. In a cohort study, the proportion of cancers in different categories or levels of exposure observed over a specific time period is compared to the proportion of cancers in a non-exposed or low-exposure comparison group observed for a similar length of time. The ratio of these two proportions (cancers in irradiated group compared to cancers in non-irradiated group) is the relative risk of cancer related to radiation exposure. In a case-control study, radiation exposure in subjects with cancer is compared to radiation exposure in subjects from the same source population without cancer. The measure of risk in a case-control study is referred to as an odds ratio, that is, the odds of having cancer given radiation exposure compared to the odds of having cancer in the absence of radiation exposure. The odds ratio approximates the relative risk.

Depending up on the level of radiation exposure, it may be necessary to include (i) large population sizes, (ii) many years of re-examination and recording of new disease (termed follow-up), and (iii) subjects exposed to a wide range of radiation doses. In order to achieve adequate statistical power[§] to evaluate risk of radiation-related cancer, the study sample size must be of a sufficiently large size. While the required sample size may depend upon a number of variables related to the characteristics of the cohort, in general, the lower the radiation dose received by the study population, the larger the population size required to determine a statistically significant radiation effect (Land, 1980). For example, the population size required to detect a statistically significant increase in the lifetime risk of cancer for whole body doses of 1 Gy would be between 1,000 and 2,000 study subjects, whereas the necessary study size might be as large as 50,000 for study subjects who had received 100 mGy whole-body dose (Brenner 2003). As an example of a recently conducted study, the 15-country study of cancer among nuclear workers enrolled 407,000 workers (average effective dose ≤50 mSv) in order to achieve adequate statistical power to evaluate cancer risk. The necessity of such a large cohort size underscored that studies of small- to medium-sized cohorts exposed to relatively low cumulative external radiation doses, will have very limited power to detect small increases in risk (Vrijheid et al. 2007).

Radiation-related cancer risk is often expressed as the excess relative risk (ERR) per unit dose or the excess absolute risk (EAR). These measures are a useful way to quantitatively summarize the risk but also facilitate comparisons across studies (UNSCEAR 2006, National Academy

[‡]In this context, confounding factors are extraneous factors that are related to both the dose and the effect (cancer risk) in the absence of dose.

[§]In this context, adequate statistical power implies a study design that can reject a false null hypothesis with a high probability.

of Sciences 2006). Both of these measures represent an increase in cancer rates compared to an unexposed population, one on a relative scale (ERR), the other on an absolute scale (EAR). An ERR of 1 refers to a doubling of the cancer rate in an exposed group compared to an unexposed group, whereas the EAR represents the cancer burden, or the additional number of cancers in the exposed population compared to the actual number of cancers in an unexposed or referent population.. For example, in the most recent report on solid cancers among A-bomb survivors, the ERR per Gy for all solid cancers in males and females combined was 0.47 per Gy (90% confidence interval 0.40–0.54) and the EAR was 52 excess cancers per 10,000 person-years per Gy (90%CI=43–60) (Preston et al. 2007).

Another measure of risk is the attributable risk, sometimes called the attributable fraction (AF) or the assigned share (AS). This measure of risk uses the ERR to calculate the number of cancers that can be attributed to exposure to radiation exposure, as described by the equation: AS=ERR / (1+ERR) (NCI-CDC 2003). The value of the AS may be particularly informative after mass radiation exposures have taken place. In such cases, local and national authorities as well as the medical profession will want to know the likely cancer burden to arise as a consequence of the exposure. One means to estimate that is through the epidemiologic concept of the AS. However, a reliable estimation of the AS depends on reliable estimates of dose to determine the ERR. While model-based estimates of dose may be useful to establishing the dose-response relationship, biodosimetry measurements could also play a key role to better estimating the expected radiation-related burden of disease.

What is meant by long-times after exposure?

As previously noted, there is usually a latency interval between the time of exposure to radiation and when the cancer is expressed, two to 10 years or more. In the case of mass-casualty events, during the early period following exposure, attention will likely be given to the possibility of acute health effects that could be lethal within a period of days to weeks. In that case, biodosimetric measurements that specifically indicate the possibility of acute health effects would be useful for the individuals suspected of having received the highest radiation doses. However, for epidemiologic studies of population groups exposed to relatively low levels of dose, especially when accumulated over long periods of time, such as the case for radiation workers without a prior history of accidental exposures (e.g., Cardis et al. 2007), biodosimetric measurements would be needed many years after initial exposure since the cancers would not be detected until that time. In contrast to the immediate situation following the Chornobyl accident (see Bouville et al. 2007) when various physical measurements of the environmental radiation field and radiation emitted from exposed persons (in the form of thyroid counts) were made to assess exposures, epidemiologic studies will take place years later. Hence, the most common attribute the application of biodosimetric measurements in epidemiologic studies is the lengthy time, often a few years to many years, between the time of radiation exposure and when the biodosimetric measurements are conducted. The requirement that the biodosimetry signal be stable for long periods of time is paramount for these purposes and must be kept in mind in developing new techniques or assessing their usefulness.

Requirements and data for retrospective dosimetry in epidemiologic studies

Exposure assessment models and strategies for dose estimation vary widely according to the problem at hand, though certain attributes of the dose reconstruction system are required for all analytic health risk studies. Moreover, understanding the capabilities and limitations of typical retrospective dose estimation techniques used in long-term health risk studies is imperative to understanding the limitations they impose on reliably estimating risk.

Methods of retrospective dosimetry for epidemiologic studies generally require three attributes (Simon et al. 2006):

- Can produce individual, reliable dose estimates to specific organs or tissues, specified by time period for protracted exposures

- Produces does estimates free of bias, and

- Can produce, or can assist in determining, quantitative estimates of dosimetric uncertainty

Following many exposure event, dose estimates may be wholly or partially based on individual radiation measurements made on study subjects, e.g., following the Chornobyl accident (Bouville et al. 2007). Even though all available measurement data are usually used in such assessments, there is often a need to supplement those data for some exposed persons with estimates from dose assessment models. When either too few individual radiation measurements are available for dose reconstruction, or when exposure assessment models are used, biodosimetry can play a role in validation of estimated doses, either on an individual basis or on a group-average basis.

The past use of individual radiation measurements to help reconstruct environmental, occupational, and medical exposures are reviewed here in a number of examples.

- In the case of environmental exposures (e.g., from exposure to the atomic bomb in Japan, radionuclide releases from the Chornobyl accident, radionuclides that contaminated the Techa River), the proportion of study subjects with radiation measurements varied widely. For example, in the case of a-bomb survivors, no individual radiation measurements were available (Kodama et al., 2001), whereas, for studies of thyroid cancer in Belarus and in the Ukraine following the Chornobyl accident, all study subjects had thyroid gamma activity measurements (Bouville et al. 2007; Hatch et al. 2005; Likhtarev et al. 2006). In the latter case, thyroid activity measurements provided information on the dose rate at the time of measurement but had to be supplemented with environmental radiation measurements and with models to account for environmental and metabolic transfer, location, and individual dietary and lifestyle habits.

- In case of occupational exposures (e.g., nuclear reactor workers, U.S. radiologic technologists, Chornobyl recovery operation workers), some personnel dosimeter results were often available but were usually not complete for the entire period of exposure, either because they were not reported or were below the detection limit at certain times. Also, the reported results did not reflect in a straightforward manner the doses to organs and tissues of interest and may have been obtained with radiation measurement devices with dissimilar characteristics. Often, the use of various types of models and data obtained from questionnaires were, therefore, necessary to derive a consistent set of doses from the reported dosimeter results.

- In the case of radiation exposures to patients with various types of medical conditions (e.g., scoliosis, cancers of the gastrointestinal tract), the amount of exposure-related information varies. For example, for therapeutic exposures, there are usually medical records of treatment doses, whereas, for diagnostic radiation exposures, there is very limited exposure information. In both cases, the exposure-related information must used as input to a model to derive the doses to the organs and tissues of interest (Stovall et al. 2007).

These various cases are all good examples of where individual radiation measurements, supplemented with dose assessment models have been required to provide the necessary dose estimates to support health risk studies. In these cases or in studies of similar design, biodosimetry could potentially supplement and improve the dose estimates.

How is biodosimetry presently being used in epidemiologic studies?

Here we are interested in how biodosimetry measurements are presently being used to contribute to the overall goals of long-term health risk studies. It may be useful to reiterate that the usual goal of such studies is to elucidate and quantify the relationship between radiation exposure and effect (e.g., cancer incidence) and that most such studies are based on population sizes of many hundreds to many thousands of persons. Quantifying cancer risks reliably necessitates obtaining good estimates of doses for many individuals. This implies that whatever type of biodosimetry measurements are used, they must be able to be carried out without excessive cost and with moderately good precision, absence of bias, and specificity to the organ or tissue of interest.

Table 1 describes selected studies of irradiated populations that have applied at least one biodosimetry measurement technique to either validate the usefulness of the method used (Kodama 2001,Tucker et al. 1997), confirm dose levels that had been derived by physical methods or measurements, such as personnel monitoring badges (Wieser et al. 2006), compare with model-based dose reconstruction (Sholom et al. 2007), or to provide biological evidence of radiation exposure among radiation workers (Bhatti et al. 2007,Jones et al. 2002). In all these cases, the biomarkers of radiation exposure had to be dose-dependent, specific to ionizing radiation exposure, and provide cumulative radiation dose, often many years after the exposure has taken place.

The two most common biodosimetry methods that have been used in epidemiologic studies are chromosome painting (fluorescent in situ hybridization or FISH) to measure the frequency of chromosome translocations, and electron paramagnetic resonance (EPR) that measures free radicals in calcified tissue of teeth. Both of these methods have been reviewed extensively (ICRU 2002, Kleinerman 2006, Simon 2007). The level of radiation exposure (high-dose vs. low-dose), temporality of exposure (acute vs. chronic), time since exposure, type of radiation (e.g. X-rays, gamma, neutron, radiofrequency), sensitivity and specificity of the assay, laboratory requirements, and availability of biological material, such as blood or teeth, are all important to choosing the best biodosimetry method for any particular study.

Due to practical considerations, such as high cost and limited availability of biological samples, only a small proportion of subjects in past studies have had biological samples analyzed, possibly with the exception of the atomic bomb survivor study, in which both FISH and EPR were validated in a larger numbers of individuals than in most other studies. Some additional examples are discussed here.

In the work of Bhatti et al. (2007), for example, FISH measurements made on lymphocytes obtained from medical radiologic technologists were used to corroborate estimation of red bone marrow (RBM) doses by models and film badge measurements. The normal large inter-individual variability of the FISH measurements at low doses prevented the confirmation of the model-based doses at the individual level. However, it was possible to demonstrate a significant dose-response relationship between the biodosimetry measurement and the model-based dose estimates that corroborated the dose estimates at the group level. The difficulties in detecting a dose-response relationship using FISH, given the relatively low mean cumulative occupational dose to red bone marrow (average of 19 mGy) and substantial inter-individual variability in translocation frequencies was overcome as a result of several methodologic strategies: a relatively large number of participants (n=152) , the scoring of many cells per person (1828 cells or 1024 cell equivalents; 277,890 cells in the whole study) and selection of participants in groups homogeneous with respect to age, smoking history, and personnel monitoring doses (film badge). In addition, those radiologic technologists who had estimated occupational film badge measurements in excess of 300 mSv were over-sampled to ensure an adequate number of persons who received doses in the upper end of the dose range.

In a study of 611 residents living in contaminated and control regions in Kazakhstan near the Semipalatinsk nuclear test site, 99 residents (16%) had biodosimetry measurements with FISH. Salomaa et al. (2002) reported that the translocation frequencies did not differ between exposed and control residents, and that previously reported model-based dose estimates on the order of 1.4 to 5 Sv could not be confirmed.

In a study of 19,000 Mayak nuclear workers employed before 1973, EPR was performed on 44 workers (only 0.2% of the cohort) (Wieser et al., 2006). The EPR doses were less than doses recorded by film badges prior to 1954, but the EPR-based doses were in agreement with film badges after 1960. Based on those differences, the investigators attributed the discrepancies in the earlier reported doses to a bias in the film badge measurements (Wieser et al., 2006).

Other studies have been useful for highlighting problems and limitations of applying biodosimetry in health risk studies. Examples include the use of EPR in studies of health effects of radiation in Southern Urals in Russia and on Chernobyl liquidators in the Ukraine (Bhat 2005) and the combined use of EPR and FISH in studies of exposures on the Techa River (Degteva et al. (2006).

Even though the proportion of the study subjects in most epidemiologic studies on which biodosimetry measurements are used is usually small, having a biologically-based dose estimate from a representative sample of the exposed study population can be useful for indicating the level of exposure of subgroups or for the overall population. The difficulty in obtaining representative samples will depend on the homogeneity of exposure within the cohort. The fact that biodosimetry is usually applied only sparsely underscores that, at present, biodosimetry rarely contributes heavily to reconstructing doses for entire cohorts under study.

While validation of model-based dose estimates is possible with biodosimetric measurements, estimation of individual dose uncertainty may still be a formidable problem. For any type of exposure, it is usually very difficult to quantitatively determine the uncertainties in individual dose estimates in a completely objective manner or to ensure that there is no bias in the dose estimates. Nonetheless, careful attention to the validation of model-based doses with biodosimetry (where possible) and a systematic application of error propagation techniques, e.g., Monte Carlo methods, can be used to quantitatively estimate the uncertainty in estimated doses.

The literature cited here suggests three primary uses of biodosimetry in health risk studies: (1) to provide estimates of radiation dose independent from analytical (model-based) dose estimates for purposes of corroboration, (2) to characterize bias in analytical dose which can potentially suggest the direction and magnitude of any needed corrections, and (3) to minimize exposure misclassification for individuals.

How might we like to use biodosimetry if better tools were available?

In the context of conducting long-term health risk studies, here we explore the question: How might we use biodosimetry if better tools were available? One obvious direction would be to use biodosimetry more frequently and more extensively in epidemiologic studies, in particular, for individual dose estimation. To realize that possibility, of course, would require techniques that are relatively simple and inexpensive to conduct and could be conducted *in vivo*, or could use easily obtained samples with a minimum of invasiveness. While attempts to corroborate model-based dose estimates with biodosimetry measurements is not new, it would desirable to make such a strategy more commonplace in different studies and within individual studies. With the proper techniques, it might also be possible to:

- Discern partial-body from whole-body exposure (with a degree of quantification)

- Discern variation of doses between organs
- Discern acute from chronic irradiation-
- Discern doses received from radiations of different quality

Desired characteristics of an ideal biodosimetry method

The characteristics that would make a biodosimetry method ideal from the point-of-view of assisting long-term health risk studies are numerous and while each attribute might have varying importance for different studies, methods should include some or all of the following attributes:

- Register the actual absorbed energy regardless of type of ionizing radiation to which it is exposed
- Have a radiation-induced signal that is stable over long periods of time (tens of years at minimum)
- Be specific to ionizing radiation
- Has a well-characterized dose-response
- Have low inter-individual variation
- Have a low minimum detectable dose (on the order of a few tens of mGy) or at least, be able to measure doses that are as low as those received by a substantial fraction of the subjects of the epidemiologic study
- Have moderately good precision (on the order of ±30%) at two-times the minimum detectable dose (and possibly better at higher doses)
- Have good accuarcy(low bias)
- Be field-friendly
- Depend on minimally invasive sampling
- Produce a measurement that directly reflect the absorbed energy in a single identifiable tissue
- Produce measurements that can be interpreted to reflect doses in other organs besides the tissue assayed
- Have low per-sample cost

In practice, all of those conditions are not met by any current biodosimetry technique. In particular, the characteristics of low invasiveness and low cost have not been met. Of these numerous characteristics, all are not equally important to all long-term health risk studies though the combination of attributes available in a particular biodosimetry method would determine its usefulness for any particular study.

CONCLUDING REMARKS

Long-term health risk studies of radiation exposure have a long historical dependence on model-based estimation of dose. In individual studies, the data available for dose estimation vary in terms of type of data, quantity and quality, though studies rarely include measurements of biological endpoints that can be quantitatively indicators of the dose. Even in those studies that have made active use of biodosimetry, the application of the biodosimetry methods has been limited to only a few percent of the entire study group. The limited use of biodosimetry can be broadly attributed to the difficulties and invasiveness of obtaining suitable samples,

instability of the dose-related signals over long periods of time, the high cost of sample analysis, and inadequate detection limits and precision at the dose levels of interest. While the purpose of this paper has been to provide a summary of the limitations of biodosimetry and to document how it has been used to-date, more importantly, it is our intent to stimulate research into the development of biodosimetric methods that can function in ways beyond just medical triage following radiation accidents. Long-term health risk studies have a fundamental importance to developing radiation protection standards and understanding radiation as a casual factor in cancer induction. These various uses all require reliable and unbiased estimates of organ-specific radiation absorbed doses on an individual basis. The application of biodosimetry in health risk studies can possibly lead to an improved understanding of radiation risks if methods can be developed that satisfy the specific needs discussed here.

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Table 1

Selected studies of irradiated populations, numbers of biodosimetry measurements conducted (translocation analysis using fluorescent in-situ hybridization (FISH) or electron paramagnetic resonance (EPR) with tooth enamel) and related information.

Study	No. of subjects	Exposure conditions	Type of biodosimetric measurement and number of measurements	Fraction of population (%) with biodosimetry measurements	Comments
Sellafield Nuclear Workers (UK)					
Tucker et al. (1997)	10,000 workers employed prior to 1976	Chronic, low-dose. Badge dosimetry available; average effective dose=130mSv	N=81 (23 with doses <50mSv and 55 w/doses >500mSv; 3 w/doses >5 and <500 mSv	~1	FISH was associated with radiation dose.
Chernobyl Cleanup workers (Russia)					
Jones et al. (2002)	>100,000	Chronic, low-dose with registered & self-reported doses	FISH=451	~0.5	Translocation frequencies were elevated by 30% in workers, and associated with radiation exposure.
A-bomb survivors (Japan)					
Kodama et al (2001)	Adult Health Study=20,000	Acute	FISH=3042 EPR=100 teeth	~16	EPR signal well correlated with chromosome aberration frequency. A highly significant and non-linear dose-response was observed for translocations with both the DS86 doses. N.B. The shape of the dose-response for cancer risk was unchanged with the DS02 doses.
X-ray Technologists (U.S.)					
Bhatti et al. (2007)	3,441 workers prior to 1950	Chronic, low-dose	FISH=152	~4.4	Translocations per 100 cell equivalents (CE): mean=1.4, S.D. ± 0.8. Red bone marrow dose: mean=1.9, S.D. ± 1.4, 0.09 excess translocations per 100 CE per Gy
Semipalatinsk Nuclear Test Site (Kazakhstan)					

Study	No. of subjects	Exposure conditions	Type of biodosimetric measurement and number of measurements	Fraction of population (%) with biodosimetry measurements	Comments
Salomaa et al. (2002)	611residents(contaminated and control regions)	Protracted, internal	FISH=99	~16	Translocation frequencies did not differ between exposed and controls. Previously reported doses on the order of 1–4.5 Gy were not confirmed.
Sholom et al. (2007)	8 villages + 1 city	Non-uniform dose distribution	EPR=102	Few %	High variability in dose estimated from teeth in same village, whereas there was less than a 2-fold difference in dose between villages basedon EPR. Model-based dose reconstruction of external doses were several times greater than village average EPR doses.
Mayak Nuclear workers (Russia)					
Wieser et al. (2006)	19,000 workers employed <1973	Protracted, internal and external	EPR=44	~0.2	EPR doses were less than available film badge doses. used prior to 1954; doses were agreement with film badges after 1960. Discrepancies in dose estimated from EPR and film badges was attributed to bias in film badge evaluations.
Bauchinger et al. (2001)	10,000 workers employed <1959	Protracted, internal and external	FISH=69	~0.7	Doses estimated from translocations were lower than doses predicted from calibration curves. Inter-individual variation of translocations was high.The usefulness of Fish as a biodosimeter was limited to <10 years after high-level protracted exposure.

Study	No. of subjects	Exposure conditions	Type of biodosimetric measurement and number of measurements	Fraction of population (%) with biodosimetry measurements	Comments
Techa River Residents (Russia)					
Romanyukha et al. (2001)	29,800 residents born <1950	Protracted, internal & external	EPR=32	~0.1	High, absorbed doses in subjects born 1945-49, attributed to high local stronium-90 concentration in enamel.