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BiodosEPR-2006 consensus committee report on biodosimetric methods to evaluate radiation doses at long times after exposure

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Review

BiodosEPR-2006 consensus committee report on biodosimetric methods to evaluate radiation doses at long times after exposure☆

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Abstract

The requirements for biodosimetric techniques used at long times after exposure, i.e., 6 months to more than 50 years, are unique compared to the requirements for methods used for immediate dose estimation. In addition to the fundamental requirement that the assay measures a physical or biologic change that is proportional to the energy absorbed, the signal must be highly stable over time to enable reasonably precise determinations of the absorbed dose decades later. The primary uses of these biodosimetric methods have been to support long-term health risk (epidemiologic) studies or to support compensation (damage) claims. For these reasons, the methods must be capable of estimating individual doses, rather than group mean doses. Even when individual dose estimates can be obtained, inter-individual variability remains as one of the most difficult problems in using biodosimetry measurements to rigorously quantify individual exposures. Other important criteria for biodosimetry methods include obtaining samples with minimal invasiveness, low detection limits, and high precision. Cost and other practical limitations generally prohibit biodosimetry measurements on a large enough sample to replace analytical dose reconstruction in epidemiologic investigations. However, these measurements can be extremely valuable as a means to corroborate analytical or model-based dose estimates, to help reduce uncertainty in individual doses estimated by other methods and techniques, and to assess bias in dose reconstruction models. There has been extensive use of three biodosimetric techniques in irradiated populations: EPR (using tooth enamel), FISH (using blood lymphocytes), and GPA (also using blood); these methods have been supplemented with luminescent methods applied to building materials and artifacts. A large number of investigations have used biodosimetric methods many years after external and, to a lesser extent, internal exposure to reconstruct doses received from accidents, from occupational exposures, from environmental releases of radioactive materials, and from medical exposures. In most applications, the intent has been to either identify highly exposed persons or confirmed suspected exposures. Improvements in methodology, however, have led many investigators to attempt quantification of whole-body doses received, or in a few instances, to estimate organ doses. There will be a continued need for new and improved biodosimetric techniques not only to assist in future epidemiologic investigations but to help evaluate the long-term consequences following nuclear accidents or events of radiologic terrorism.

Keywords: Dosimetry; Biodosimetry; Retrospective dosimetry

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1. Introduction

Retrospective dosimetry is the set of methods for estimating radiation doses that have been received in the past. The type of dosimetric quantity estimated (e.g., air kerma, organ absorbed dose, effective dose, etc.), how specific the dose estimate is to an identifiable person, and the obtainable precision of the estimates can vary widely depending on the purposes of the dose estimation and the techniques used. Various available assays are discussed in this paper and for any particular case the choice of the most appropriate technique to employ will depend on several factors. Possibly the most important factor is the elapsed time between exposure and analysis because the quality of the data obtained depreciates differentially among the various assays.

In the context of national security needs, the BiodosEPR-2006 conference created two consensus committees, this committee to evaluate methods of retrospective dosimetry suitable for estimating radiation doses at long times after exposure, and a second committee to evaluate methods in the very near term after exposure. As a means of distinguishing the charges of these committees, we have defined "long times after exposure" to be 6 months at a minimum, but it can extend to many years. Experience, thus far, has been limited to about 50 years. Moreover, this committee has focused its analysis on methods of biodosimetry, which, as commonly understood, are methods of measurement of biological samples that are used to estimate doses without resorting to the detection of ionizing radiation. An exception has been made to include, within the scope of the discussion, the luminescence techniques (thermoluminescence, TL, and optically stimulated luminescence, OSL) that are applied primarily to building materials and artifacts to measure cumulative external dose. These techniques provide complementary dosimetry data for dose reconstruction studies. However, OSL has been applied to tooth enamel and this type of application is more closely related to the biodosimetric methods discussed in this paper.

Other measurement techniques used for the purpose of retrospective dosimetry involve the detection of ionizing radiation: they include (1) Bioassay methods, in which biological samples (e.g., urine and feces) are measured; (2) ex vivo methods, in which the ionizing radiation emitted by various parts of the body (e.g., thyroid) is detected; and (3) physical methods, in which environmental, non-human, samples are measured. Those methods of retrospective dosimetry are not discussed in this paper.

Dosimetric methods to estimate radiation exposures that have taken place in the past can be classified into theory-based methods (i.e., analytical dosimetry) in which models are extensively used to relate the dose to the source of exposure, and measurement-based methods where the individual dose is derived from measurements in man or from a quantity closely related to the dose. The choice of a method is largely determined by the circumstances of the exposure including the type of radiation and the degree of exposure, how long ago the exposure took place, and the type, quality, and amount of relevant input or measurement data that are available. In addition, it is frequently the case that both types of methods support each other, that is, analytical methods use measurements for validation or calibration purposes, while measurement-based methods require some analysis to infer the dose from the measurement. In the context of national security needs, i.e., preparing and responding to accidents and terrorism events, both analytical and measurement-based dosimetry methods will undoubtedly be needed.

The need for biodosimetry stems from societal and technical needs, and research initiatives including: (1) the estimation of high doses resulting from past medical, occupational, and environmental exposures, (2) triage activities following radiation accidents or terrorist events, and (3) research purposes (e.g., epidemiologic studies).

While medical triage of individuals exposed to potentially life-threatening radiation doses is an obvious use of

retrospective dosimetry, methods suitable for "times shortly after exposure" will fulfill that function. Biodosimetry at long times after exposure is typically used for very different purposes, two primary uses are to support long-term health risk (epidemiologic) studies or to support individual or group compensation claims. At a minimum, epidemiologic studies require hundreds of study subjects to achieve the necessary statistical power, and thousands of study subjects is not unusual. Biodosimetry measurements, in theory, could replace analytical dose estimates in epidemiologic studies, though, typically, it is not possible to acquire enough biologic samples or too expensive to make enough measurements to completely replace model-based dose estimates. For that reason, biodosimetric measurements seem likely to continue to play supportive roles in epidemiologic studies, though technical advances may change that outlook. Biodosimetry also has the potential to be used to evaluate the presence of bias in model-based dose estimates, even to the point of possibly suggesting bias correction factors. Such a function, however, has not yet been widely applied.

This committee has attempted to consider a wide range of expertise and literature related to retrospective dosimetry to evaluate the presently available biodosimetry methods in the context of dose estimation at long times after exposure. From that evaluation, a consensus viewpoint of this committee is presented on the usefulness of the presently available techniques, as well as the future needs.

2. Methods

Presented here are brief descriptions of the four methods of retrospective biodosimetery considered in this report: electron paramagnetic resonance (EPR), cytogenetics (FISH), somatic cell assays (GPA), and thermal and optically stimulated luminescence (TL/OSL).

2.1. Electron paramagnetic resonance

Electron paramagnetic resonance (EPR; also known as electron spin resonance or ESR) spectrometry is a physical method capable of measuring the concentration of stable radiation-induced radicals in materials. EPR measurements of exposed samples can be used for retrospective assessment of the absorbed dose and are referred to as EPR dosimetry. An introduction to the method and a survey of applications can be found in Ikeya (1993). The mineral component of bones and teeth (hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$) is a suitable probe for use in EPR dosimetry and for reconstruction of individual dose. Following radiation exposure, stable CO_2^- radicals are created out of the CO_3 impurities in the hydroxyapatite crystals (Moens et al., 1993). Tooth enamel as a radiation detector has been known for almost four decades (Brady et al., 1968). It is the best tissue for dosimetry because no other tissue in the body has such a high content of the hydroxyapatite (94–97%) (Driessens, 1980).

The application of the EPR technique to the problem of retrospective dosimetry has certain valuable properties:

- Detected EPR signal results only from radiation exposure.
- Dose response is extremely stable with time, more than 10^6 years (Swartz, 1985; Skinner et al., 2000).
- Dose dependence in the dose range of interest is linear (up to 100 Gy).
- Readout of signal is non-destructive, allowing for measurements to be repeated an unlimited number of times.
- Little individual variation of radiation sensitivity (Wieser et al., 2001), which allows a universal calibration for dose determination.
- Tooth enamel as a dosimeter is sensitive to all types of ionizing radiation and UV, though it has relatively low sensitivity to neutrons.

An evident weakness of the method is that the measurement is currently performed ex vivo, i.e., on extracted or exfoliated teeth. Consequently, only individuals who have lost teeth as result of dental disease can be investigated by EPR dose reconstruction. In vivo measurement methods are being developed, but improvements are still needed (Miyake et al., 2000; Zdravkova et al., 2003; Swartz et al., 2005). Not all types of teeth are suitable for EPR dose measurement to the same degree. For example, front teeth can show an overestimated dose due to the exposure to sunlight (Liidja et al., 1996; Ivannikov et al., 1997; Nakamura et al., 1998a, b; Sholom et al., 1998; Nilsson et al., 2001; El-Faramawy, 2005); diseased or restored parts of teeth present confounding factors (Sholom et al., 2000) and are usually rejected; teeth with enamel mass smaller than about 50 mg can be inadequate for reliable dose assessment and require special procedures (Hayes et al., 2000). If dose of exposed children has to be measured, naturally lost milk teeth can be used (El-Faramawy and Wieser, 2006).

An EPR dose measurement protocol consists of several primary steps (Romanyukha and Regulla, 1996). In particular, sample collection, classification and selection are important steps in the dose reconstruction process and require careful planning. As much information as possible about personal data (residence, birth date), medical and occupational exposure, and dental restorations, should be collected. Sample preparation for EPR measurements starts by isolating enamel (the hard outer shell of the tooth) from the dentine which comprises the inner bulk of the tooth tissue. This can be done through chemical or/and mechanical procedures.

Dose estimates are derived from the measurements of the EPR radiation-induced signal intensity (or its peak-to-peak amplitude) using a calibration in radiation absorbed dose units. The necessary instrumentation, e.g., the EPR spectrometer and sample preparation tools, is expensive and requires well-trained and skilled operators. The applicability of the method presently is consequently limited to a small number of expert laboratories.

Due to the long signal stability, the tooth maintains a cumulative memory of every exposure that occurred during the individual's life. Hence, the dose of a single accidental event has to be extracted from the lifetime-accumulated dose through

subtraction of other dose contributions, such as natural background, occupational, or medical exposures. These other dose contributions have to be estimated by independent methods, e.g., the natural background exposure can be evaluated by the dose rate in the region of residence and the tooth age and medical or occupational radiation exposures may be estimated by an interview of the tooth donor about his/her radiation history. If it is known that bone seeking radionuclides like ^{90}Sr were incorporated in teeth tissues to a significant extent, an independent measurement of the concentration of ^{90}Sr in teeth needs to be carried out in order to determine the relative contributions from external exposures and internal contamination (Romanyukha et al., 2001; Veronese et al., 2006). Göksu et al. (2002a, b) and Shishkina et al. (2005) have shown that the ^{90}Sr concentration in dental tissue can be measured using passive beta detectors; a good correlation with the measured EPR values was obtained in their experiments.

While the EPR method measures the dose absorbed in tooth enamel, the conversion from tooth dose to effective or organ dose is determined mathematically by simulation of the radiation transport in the body, taking the exposure conditions into account (Takahashi et al., 2002; Ulanovsky et al., 2006). Knowledge of how the EPR signal depends on the radiation type and energy is required. This has been widely investigated for photons and neutrons (Bochvar et al., 1997; Aldrich and Pass, 1988; Aragno et al., 2000; Wieser et al., 2002; Fattibene et al., 2003; Ivannikov et al., 2004; Trompier et al., 2004). It should also be noted that additional irradiation of tooth enamel may be caused by beta particles emitted by radionuclides incorporated into soft tissues of mouth. This factor should be accounted for to achieve correct interpretation of EPR dosimetry estimates (Stepanenko et al., 2003).

There are possibilities for improvement of EPR dosimetry technology which could allow dose measurements to be made in vivo using L-band (1 GHz). It has been also suggested to use very small amounts of tooth enamel ($\sim$ 2 mg) for the measurements in Q-band (34 GHz) (Romanyukha et al., 2004). Recent experiments have shown that the dose threshold in Q-band can be as low as 200 mGy for a 2-mg sample. It is quite possible that in the near future EPR spectrometers with higher sensitivity will use smaller sample mass and make measurements faster.

2.2. Cytogenetics

The lymphocyte dicentric assay is the traditional cytogenetic method for biological dosimetry, though it has long been realized that the signal is transitory (Bender et al., 1988). The dicentric's persistence is a function of the rate that the exposed person replaces her or his phytohaemagglutinin-responsive T-lymphocytes and, inevitably, there are individual variations related to factors such as age, infections, hemorrhage, lifestyle, and the magnitude of the exposure itself. Nevertheless, for persons irradiated to levels below the range that would impair haematopoiesis, an exponential disappearance of dicentrics from the peripheral circulating pool occurs. A "rule of thumb" for the rate of decrease is a half-time of approximately 3 years (IAEA, 2001). Some cases that have been followed up have supported that value (e.g., Lloyd et al., 1998) but, especially where high doses have been received, a more rapid decline in dicentrics has been reported (Pressl et al., 2000; Sevan'kaev et al., 2005). Therefore, in general, the dicentric assay is not appropriate for retrospective dosimetry at long times after exposure. For applications of the dicentric assay which tends to be used soon after exposure, but may also be used with corrections for elapsed time, and which may be adapted for rapid response triage, the reader is referred to the report of the BiodosEPR-2006 Committee on Acute Dosimetry (Alexander et al., 2007).

Some chromosome aberrations, particularly translocations, pass more readily through cell division and, therefore, persist longer than dicentrics. Cells bearing translocations were observed in descendant lymphocytes of originally irradiated stem cells, as shown in the classic follow-up study of ankylosing spondylitics (Buckton et al., 1967), which led to the designation of unstable (Cu) and stable cells (Cs), with much longer persistence of the latter. However, identification of translocations required karyotyping, and before chromosome banding was established, this was an impractical approach for biological dosimetry. Until the development of fluorescence *in situ* hybridization (FISH) with whole chromosome paints, the dicentric was used for assessing dose in cases involving up to several years after exposure or for protracted exposures. In those cases, the 3 year approximation of the half-time provided credible dose estimates (Sevan'kaev et al., 1995).

Today the preferred translocation assay uses chromosome painting in which multiple pairs of chromosomes are labeled, often in multiple colors. Much effort has been expended to optimize protocols for employing chromosome painting as a retrospective biodosimeter and defining its limits of applicability (Edwards et al., 2005). Full karyotyping or banding by FISH are still too expensive and time consuming for routine application although these techniques markedly improve the detection of chromosomal insertions and inversions, which can additionally provide a "fingerprint" for exposure to high LET radiation (Anderson et al., 2003; Hande et al., 2003).

Routinely, a limited number of the larger pairs of chromosomes are highlighted in one or a few colors and, depending on the combinations, this provides efficiency in detecting translocations (Johnson et al., 1999a, b; Moore and Tucker, 1999; Jones et al., 2002). For example, 20% of the genome painted in one color provide an efficiency of 32%, and two sets of three chromosome pairs painted in different colors provides an efficiency of 56%. If it is required to compare or combine data from different painting combinations, the formulae of Tucker et al. (1997a, b) have been shown to give acceptable conversions to full genome equivalence. It is agreed that centromeres should be clearly visible to distinguish dicentrics from translocations (Nakano et al., 1993); for this purpose, a specific pan-centromere probe can be included if desired. However, such probes label the pericentromeric heterochromatic DNA and not the centromere itself, and their use may lead to the misdiagnosis of exchanges if rearrangements occur within the labeled region. For that reason, many investigators rely on chromosome morphology for centromere identification.

Experience has shown that to estimate low doses, as many as 1000 whole genome equivalents should be scored for each exposed person. Scoring of fewer cells may be sufficient for evaluating high doses. The number of cells that should be scored may also depend on the ages of the subjects and each person's smoking history, as both age and smoking are known to increase the baseline frequency of translocations (Ramsey et al., 1995).

At least two key decisions are important in the analysis of cells for chromosome aberrations. The first decision concerns whether or not to score a particular cell. Criteria for the inclusion of cells for analysis have been published (Tucker et al., 1997a, b) and these criteria should be accepted prior to reading the slides. At a minimum, the centromeres from all the painted chromosomes should be present in the metaphase. Some investigators use a more stringent criterion and include in the analysis only those cells that contain all the chromosomal material since there is evidence that missing material may lead to abnormally high translocation yields when considering low-induced frequencies near control levels (Edwards et al., 2002). Investigators who elect to include all the abnormal cells in their analysis (even if, for example, a terminal deletion is present in one chromosome) do so out of concern that selective elimination of cells may lead to an underestimate of the true dose, especially in situations where considerable time has passed after the exposure. Under these conditions, many of the cells will have undergone multiple mitoses following the initial induction of aberrations, leading to loss of some material that was initially associated with unstable aberrations. This brings us to the second decision, which concerns determining which aberrations best relate to retrospective radiation doses. Some researchers record one- and two-way translocations separately, because two-way translocations are known to be more stable with time (e.g., Lindholm et al., 1998; Tucker et al., 2005a, b). An approach used by other investigators is initially to record every aberrant chromosome in every cell using an established nomenclature system such as PAINT (Tucker et al., 1995) and then, subsequently, use archived photographs to re-code the cells into one-way and two-way translocations. The re-coding required in this approach is typically accomplished by a second experienced cytogeneticist. The recoding step also affords the opportunity to perform quality control checking of all the cells.

Improvements in the resolution of molecular hybridizations and the inclusion of telomere probes (Fomina et al., 2000) have shown that many of the apparently one-way translocations are, in reality, reciprocal. Hence, both types of translocations may be utilized for dosimetric purposes. This observation is supported by an in vitro study on the persistence of translocations (Tucker et al., 2005a, b). Early investigators recorded only those aberrations that involved the painted chromosomes. However, some investigators (e.g., Rodriguez et al., 2004) have also examined the counterstained chromosomes to distinguish stable from unstable (Cs from Cu) cells using full genome information. Realizing that lymphocytes sampled many years after irradiation are derived from exposed stem cells, it is generally only the stable daughter cells from the irradiated population that have survived through subsequent divisions. In practice, at long times (i.e., many years) after exposure, the frequency of unstable (Cu) cells will have been reduced to near control levels but, particularly for shorter time intervals, irradiated Cu lymphocytes will also be among the scored cells. Those observations led to the suggestion that translocations in stable (Cs) cells should be measured. When that was done, translocation frequencies for an individual showed better constancy with increasing time (Lindholm and Edwards, 2004).

High dose exposures tend to be recognized promptly due to early clinical signs, and in those situations, the dicentric assay is appropriate for dose estimation. However, late discovery of an exposure, of perhaps a month, is not unusual, and by that time, peripheral lymphocyte counts may have sharply declined and dicentric persistence is questionable. An accident in Istanbul (IAEA, 2000) is an example where FISH painting was used retrospectively after 1 month and showed that dicentrics underestimated the doses by possibly 25%. It is generally expected that chromosome painting (FISH) is useful for retrospective discrimination of exposures having taken place at more distant times in the past and at relatively lower levels, i.e., well below the threshold for overt clinical reactions. In such situations, there are considerable constraints to its application due to two factors, the accuracy with which the linear term of the dose response calibration is known, and the control (background) frequency of translocations. Currently those two factors are probably the major limitations to the sensitivity of the FISH method.

Calibration of the FISH method is made by in vitro irradiation of blood samples with the assumption that their radiosensitivity equates to stem cells of the daughter lymphocytes sampled from the irradiated person. There are now a number of published dose response curves, albeit not all confined to Cs cells. Few data sets have well characterized the linear yield coefficients because of the need for large numbers of cells to be scored in the low dose range (< 0.5 Gy). There is now a consensus view that reciprocal translocations and dicentrics are induced with more-or-less equal frequency (Bauchinger et al., 1993; Nakano et al., 1993) and so as an interim measure until better calibration data are available, it has been suggested that one may infer the low dose-induced translocation frequency from the better characterized linear coefficient for dicentrics (Finnon et al., 1995).

Because translocations persist, it is not surprising that their background frequency rises with donor age as has been effectively shown by Ramsey et al. (1995) and Whitehouse et al. (2005). Therefore, when undertaking retrospective dosimetry, a generic age-linked background must be assumed. Even allowing for age, there is still additional variation in translocation frequencies in unirradiated control subjects. Some of this variation is probably due to cigarette smoking but, to date, no other confounding factor has been identified in any convincing way.

2.3. Somatic cell assays

Ionizing radiation can induce mutations in human somatic cells and accumulation of somatic cell mutations in humans has been linked to carcinogenesis. While several laboratory-based assays have been developed to characterize mutations that have

been linked to carcinogenesis, few of these assays have been successfully translated into successful biodosimetry tools.

The glycophorin-A (GPA) somatic mutation assay method was developed to provide a reliable and quick method to detect and measure induced somatic cell mutations in humans that were exposed to ionizing radiation. GPA was first applied to the A-bomb survivors and found to be relatively well correlated with physically based dose estimates (Langlois et al., 1987; Kyoizumi et al., 1996; Nakamura et al., 1991). Since that time, it has been principally applied to populations exposed to radiation from accidents (Straume et al., 1992; Jensen et al., 1995; Bigbee et al., 1996, 1997; Jones et al., 2002). Because the assay requires a small amount of blood and can be performed relatively quickly, it was thought that GPA would be suitable for identifying genotoxic exposures in large populations.

Glycophorin-A is a glycoprotein that is expressed on the cell surface of red blood cells and it occurs in two allelic forms, M and N. This somatic mutation assay uses a flow cytometric technique in which the glycophorin-A protein is labeled with fluorescent monoclonal antibodies that are specific for individual allelic forms. The assay measures variant frequencies in the cell types and the variant frequencies serve as a quantitative indicator of radiation dose; the higher the frequency, the higher the cumulative radiation dose. Several comprehensive reviews of the GPA assay and its application to radiation-exposed populations are available (Nakamura et al., 1991; Albertini and Hayes, 1997; ICRU, 2002).

The GPA assay has several practical advantages. Only 1 ml of blood per subject is required. Blood collected from study subjects can be stored at refrigerator temperature (4 °C) up to 1 week prior to analysis making it useful in studies with limited field conditions. The GPA assay can be performed on a commercially available flow cytometer, reducing the amount of labor and time, which makes it attractive for large population studies.

A major limitation of the GPA technique is that only 50% of the general population is M/N heterozygous and, therefore, eligible for the assay. In a recent review of the usefulness of the GPA assay as a biological dosimeter of cumulative radiation exposure, the International Commission on Radiation Units and Measurements (ICRU, 2002) concluded that the GPA assay is not suitable for individual dose assessment, because of the inter-individual variability of variant frequencies at similar doses, though the assay can be used to determine average doses in population groups. Although the GPA assay has several practical advantages as a biological dosimeter, it does not appear to be useful as a biological dosimeter for external radiation doses less than 1 Gy. The assay may be useful in studies of populations exposed to higher radiation doses, especially when used in combination with other biological markers to characterize the level of radiation exposure.

2.4. Luminescence

The method of luminescence retrospective dosimetry is based on the stimulated release of energy acquired and stored in the dosimetric material during the irradiation phase. The energy is released as visible light (luminescence). If the stimulation is by absorption of heat, the process is thermoluminescence (TL), and if the stimulation is by absorption of light, the process is optically stimulated luminescence (OSL). Both TL and OSL are members of a family of stimulated phenomena described in full in various published texts (e.g., Oberhofer and Scharmann, 1981; Horowitz, 1983; McKeever et al., 1995; Bøtter-Jensen et al., 2003).

The energy is absorbed in the dosimetric material via the processes of pair production, Compton scattering or the photoelectric effect (depending upon the radiation type and energy), resulting ultimately in ionization and the trapping of electrons and electron holes at defect sites within the material. In this way, energy is stored in the material proportional to the radiation energy absorbed, i.e., proportional to the dose of radiation delivered. Subsequent stimulation of the sample (via heat for TL or light for OSL) leads to a luminescence signal, which, in favorable circumstances, is proportional to the absorbed dose, providing a means of dosimetry.

TL is widely applied to measure individual occupational exposures, using high-sensitivity, artificially grown crystals. For retrospective dosimetry, however, the choice is limited to commonly used materials. Suitable dosimetric materials for luminescence are generally any inorganic (or even organic) insulator. For retrospective dosimetry, the main materials of interest are naturally occurring minerals such as quartz and feldspar within building materials (bricks, tiles), or other ceramic objects, such as glass, pottery, porcelain fixtures, etc. (ICRU, 2002; Bøtter-Jensen et al., 2003; Young and Kerr, 2005). Suitable materials can also include semiconductor devices carried as personal items (Göksu and Bailiff, 2006). Appropriate preparation of the materials is required; multiple- or single-aliquot techniques have been variously used over the years to evaluate the absorbed dose in these materials (Bøtter-Jensen et al., 2003). The dose evaluated is most accurately described as the "beta dose equivalent", which is the dose of beta irradiation that gives the same TL or OSL signal as the signal due to the natural or "accident" exposure by gamma radiation.

The beta dose equivalent (D_e) is equal to the natural dose due to naturally occurring radioisotopes (primarily, uranium, thorium and potassium) and cosmic rays absorbed over the lifetime of the object, plus the dose due to the accident. Evaluation of the accident dose, therefore, requires a determination of the natural dose rate and the age of the object. Thus, the accident dose (D_x) is given by

$$D_x = D_e - t(D'_\alpha + D'_\beta + D'_\gamma + D'_c)$$

where t is the time since manufacture of the object, D'_α, D'_β and D'_γ are the dose rates from uranium, thorium and potassium due to alpha, beta and gamma irradiation, and D'_c is the dose rate due to cosmic radiation.

Whereas electron EPR is applied to determine the absorbed dose in a biogenic mineral within humans (i.e., tooth enamel), luminescence techniques are used to measure the absorbed dose in artifacts (building materials, household materials, etc.) associated with human occupation and activity. In these

circumstances, the primary purpose of the luminescence method is consequently not to infer the dose to individuals, but to elucidate the dosimetry of the environment of the irradiated population. In this way, luminescence data derived from artifacts can contribute to the dose assessment of populations or groups of individuals by providing benchmark values of cumulative absorbed dose for computational modeling simulations for dose reconstruction of the Hiroshima and Nagasaki bombings and settlements contaminated by fallout or accidental exposure to radiation sources (IAEA, 1998; Young and Kerr, 2005; Cullings et al., 2006; Stepanenko et al., 2006b).

Where the method is applied to brick buildings facing contaminated ground, the cumulative dose in brick due to external gamma radiation can be converted to dose in air for comparison with the data employed in the computational modeling referred to above. Such conversion (Bailiff et al., 2004a, b, 2005) is usually based on Monte Carlo simulation of the transport of gamma radiation emitted by radionuclides in soil and the deposition of energy in the bricks that make up the walls. The simulations allow coefficients to be derived that relate absorbed dose in a specified volume of brick to dose in air at a reference location, leading to the derivation of conversion factors. The reference location, devised for computational modeling work, is the dose in air at a height of 1 m above soil that is uniformly contaminated with radionuclide sources. The simulations also provide a means of adjusting the conversion factors for the effects of heterogeneous distribution of fallout in the vicinity of the sampled building. So far, demonstration of this approach has been performed for a source energy of 662 keV, but simulations for other source energies have been performed (Bailiff et al., 2005). The absorbed dose to luminescent minerals within the sub-surface of a brick in a wall (at a height of 1 m and facing uniformly contaminated ground) is about half of the dose in air at the reference location (i.e., similar to that expected on the basis of irradiation geometry alone). This proportion changes with depth in the wall due to the effect of attenuation and also with elevation (ICRU, 2002). The adjustments for heterogeneity are based on either dose-rate monitoring in the field or on the measurement of the residual source activity in soil. Where the extant source activity cannot be detected, the uncertainty in past source distribution needs to be assessed when translating absorbed dose values from wall to a reference location. However, careful selection of multiple samples can be used to test assumptions made concerning the source distribution (Bougrov et al., 1998; Bailiff et al., 2004a, b). The geometry and configuration of the sampled buildings and walls are very important for correct Monte Carlo calculations of the conversion factors from absorbed dose in a specific volume of brick to dose in air at a reference location. Hence, the careful documentation of geometry and configuration of sampling buildings and locations is needed (Young and Kerr, 2005; Stepanenko et al., 2006c).

The currently developed techniques are capable of determining cumulative absorbed doses from $\sim$ 10 mGy to tens of Gy (i.e., well beyond the range of interest in epidemiologic studies) using quartz extracted from modern bricks. However, as indicated above, a dose due to gamma radiation arising from the introduction of artificial sources is obtained after subtraction of the dose due to natural sources. The resolving power of the method depends on the relative size of each dose contribution. For example, in a 15 year-old brick where the cumulative dose is 100 mGy and where half the dose is due to natural background sources, the overall uncertainty in the dose due to artificial sources is expected to be about $\pm$20%.

Because TL and OSL are most frequently applied to building and non-biologic materials, they are usually not considered as biodosimetry techniques. However, OSL can be applied to tooth enamel (Godfrey-Smith and Pass, 1997; Yukihara et al., 2007). In a broader context, however, TL and OSL can both supplement analytical dosimetry estimates of individual or group dose and for that reason are considered in this paper for discussion and comparison.

2.5. Emerging biodosimetry techniques

There are several emerging biodosimetric techniques that are based on previously known markers of exposure, e.g., stable chromosome aberrations and stable radiation-induced radicals in tooth enamel or stable radiation-induced defects in quartz contained in building materials but measured with newer technologies. To take further advantage of these markers, new measurement technologies are being developed for assessment of stable-radiation induced radicals in tooth enamel, for in vivo EPR measurements of tooth enamel using the L-band, and for OSL of tooth enamel. In addition, there are some techniques for determining the internal dose contribution to teeth. Each is briefly described here.

2.5.1. In vivo EPR measurements in teeth using L-band (1.2 GHz)

L-band EPR systems use a lower microwave frequency than X-band. The lower frequency makes EPR measurements less perturbed by high water content in a sample and allows the use of larger samples, e.g., whole teeth. The first demonstration of the capability to carry out in vivo EPR measurements in L-band was reported in 2000. In spite of the existence of some commercial models of L-band EPR spectrometers, in vivo measurements of teeth introduce special design problems; for example, resonators and a magnet system are needed that can comfortably and effectively encompass the human head. In its current state, the in vivo EPR dosimeter can measure doses only as low as 1 Gy.

2.5.2. OSL of teeth and other materials

The OSL technique uses light to stimulate a radiation-induced luminescence signal from materials previously exposed to ionizing radiation. In general, this luminescence originates from radiation-induced defects in insulating crystals and is proportional to the absorbed dose of radiation. The OSL technique has been successfully used for personnel dosimetry using high-sensitivity, artificially grown crystals, and for sedimentary dating using natural crystals. Godfrey-Smith and Pass (1997) first suggested the possibility of using OSL with dental

enamel. Recently, the detection limit of OSL and human tooth enamel has been shown under laboratory conditions to be 4–6 Gy (Yukihara et al., 2007), though further improvements in lowering the detection limit are expected.

2.5.3. Techniques for internal dose

Two new techniques have recently been developed to measure ^{90}Sr in teeth that allow for the separation of external and internal dose contributions in total absorbed dose in tooth enamel. One is based on the OSL measurements of an imaging phosphor plate that is attached to the tooth for several hours. This procedure allows an accurate mapping of the distribution of ^{90}Sr (or other radionuclides) in the teeth. This method can be used as an individual indicator of radionuclide intake. Its advantages are its high sensitivity (0.02 Bq/g/mm^2 of ^{90}Sr), its ability to examine small detectable cross-sectional areas of dental tissue (dentin) contaminated with ^{90}Sr (from 0.01 mm^2), its non-destructive aspect, and its simplicity of use. The combined application of this method with EPR tooth biodosimetry can provide more accurate dose estimates when there is both internal contamination and external dose. The second technique uses a single grain OSL attachment system for assessing the spatial distribution of radionuclides incorporated in human teeth. Detectors containing arrays of single grains of alpha-Al_2O_3:C powder, which can accommodate 100 single grains in 0.3 mm holes, are positioned on a 10 × 10 grid. This system, however, is less sensitive than the imaging plate and, therefore, requires longer time for measurements.

3. Historical use of biodosimetry in dose reconstructions and epidemiologic studies

Biodosimetry, as discussed, can contribute important, independent estimates of cumulative radiation exposure in epidemiologic studies for individuals and population groups, especially in studies where physical dosimetry measurements are incomplete or lacking altogether or where the usefulness of analytical dosimetry is limited by high uncertainty. The biological markers that have been applied most frequently to irradiated populations following environmental, occupational or medical ionizing radiation exposure include the dicentric assay and the fluorescent *in situ* hybridization (FISH) method for chromosome translocations, both using peripheral blood lymphocytes, glycophorin-A somatic mutation assay (GPA) of red blood cells, and EPR of tooth enamel. The application of specific biodosimeters in these populations depends upon the level of exposure (high-dose vs. low-dose), mode of exposure (acute vs. chronic), time since exposure (recent vs. more distant past), type of radiation (e.g., X, gamma, beta or neutron), sensitivity and specificity of the assay, laboratory requirements, and availability of blood or teeth. Used less, but still relevant are measurements of TL or OSL in building materials of residences and workplaces of the exposed populations.

More than one dosimetry technique has been applied to A-bomb survivors, Chernobyl clean-up workers, Techa River residents, populations living near the Semipalatinsk nuclear test site, and some radiation accident victims (Nakamura et al., 1998b; Degteva et al., 2005; Sevan'kaev et al., 2006). Combinations of two biodosimeters (usually FISH and GPA) have been applied to nuclear workers and radiation accident victims with TL/OSL having been primarily applied to populations exposed to radioactive fallout. The circumstances in which the four biodosimetric techniques have been applied are summarized in Table 1, along with dose estimates based on physical measurements, biodosimetry, or both.

Each dosimetry technique has unique advantages and limitations depending upon the level and type of radiation exposure. In some cases, the techniques have been used exclusively for dose reconstruction; in other cases, the techniques have been used to support long-term health risk studies. Following is a more detailed discussion of the published uses of each technique as applied to epidemiologic studies.

3.1. Use of EPR in epidemiologic studies

EPR dose reconstruction has been used to validate radiation exposure models, specifically to predict doses from radiation accidents or to determine environmental exposures. EPR dose reconstruction has been used for epidemiologic studies of the atomic bomb survivors (Nakamura et al., 1998a, b), Chernobyl accident (Ishii et al., 1990; Chumak et al., 1999; Skvortsov et al., 2000), Techa River population (Romanyukha et al., 1996, 2001; Degteva et al., 2005; Tikunov et al., 2006), Mayak nuclear workers (Romanyukha et al., 2000; Wieser et al., 2006b), Lilo accident victims (Cosset et al., 2002), Turkish accident victims (Gunalp et al., 2002) and the Semipalatinsk population exposed as a result of nuclear tests (Ivannikov et al., 2006; Stepanenko et al., 2006c). In the framework of several projects from all over the world, international intercomparison programs on EPR tooth dosimetry have been carried out since 1993 (Bailiff and Stepanenko, 1996; Chumak et al., 1996; Wieser et al., 1996, 2000, 2005, 2006a; Hoshi et al., 2006; Ivannikov et al., 2007). EPR measurements of tooth enamel have been recognized as a reliable method for retrospective assessment of individual doses (IAEA, 2002; ICRU, 2002) and comparisons of dose in tooth enamel with data from other sources have been carried out (e.g., SOUL, 2005; Stepanenko et al., 2006a).

As mentioned previously, the reconstruction of doses obtained by both EPR and FISH for 100 survivors of the atomic bombs was closely correlated with estimated radiation dose (Nakamura et al., 1998b) and, thus, demonstrated the usefulness of EPR for acute exposures.

With regard to the Chernobyl accident, doses to several thousand individuals were reconstructed by EPR including different groups of Ukrainians and Russians residing in radioactively contaminated areas, as well as clean-up workers at the Chernobyl site. The EPR reconstructed doses to individuals exceeded doses estimated from background levels, e.g., up to 70 mGy for populations of some radioactively contaminated villages (Stepanenko et al., 2003). EPR also revealed a mean whole-body dose of 160 mGy for clean-up workers (Chumak et al., 1999).

The Techa River population was exposed to radioactive waste released into the river during the early 1950s. EPR dose reconstruction with teeth from Techa riverside residents revealed very high doses (up to 15 Gy) absorbed in tooth enamel for individuals born in 1945–1949 (Romanyukha et al., 2001), whereas reconstructed doses for tooth donors born in other years were a factor of 50 lower. The former observation can be explained by the younger age of the donors born 1945–1949. Strontium-90 (^{90}Sr), which contributed about 12% of the radioactive releases into the Techa River, accumulates in teeth and bone. Therefore, individuals who had teeth formation during the radioactive releases (1945–1949) accumulated a much higher amount of ^{90}Sr than other exposed individuals in that population. This finding suggests the ability of EPR dose reconstruction in teeth collected from donors of different ages to determine both the doses and type of radionuclide intake (Romanyukha et al., 2002a, b).

EPR dose reconstruction with teeth from Mayak nuclear workers showed relatively good agreement between EPR derived doses and individual dose monitoring (Romanyukha et al., 2000), depending upon the type of badge and specific plant at Mayak (Wieser et al., 2006b). The existence of reliable dosimetric information for Mayak nuclear workers made the results of the independent EPR dose reconstruction study valuable. It established an important bridge between doses measured by individual dosimeters and dose reconstruction estimates (Hoshi et al., 2006).

The Semipalatinsk population was exposed to radioactive fallout as a result of nuclear tests (456 nuclear explosions in the period between 1949 and 1989) (Mikhailov, 1996). EPR measurements in teeth of inhabitants near the test site have been underway for several years (Romanyukha et al., 2002a,b; Ivannikov et al., 2006; Stepanenko et al., 2006c; Sholom et al., 2007) in support of epidemiologic investigations and will additionally provide insights into the reliability of theoretical models for dose reconstruction (Stepanenko et al., 2006a).

3.2. Use of FISH in epidemiologic studies following whole-body exposures

Whole-chromosome painting for radiation biological dosimetry has been applied to many exposed populations. Among these are the Japanese A-bomb survivors (Kodama et al., 2001), Chernobyl liquidators (Salassidis et al., 1994; Moore et al., 1997; Littlefield et al., 1998; Jones et al., 2002), Sellafield British Nuclear Fuels workers (Tucker et al., 1997a, b; Tawn et al., 2000, 2004), Mayak nuclear workers (Salassidis et al., 1998; Bauchinger et al., 2001; Burak et al., 2001), residents living near Techa River (Bauchinger et al., 1998) and the Semipalatinsk test sites (Stephan et al., 2001; Salomaa et al., 2002), residents of buildings contaminated with ^{60}Co in Taiwan (Chen et al., 2000), radiation accident victims in Goiania (Straume et al., 1991; Natarajan et al., 1998; Camparoto et al., 2003), astronauts (George et al., 2005), as well as medical radiation workers (Verdorfer et al., 2001; Montoro et al., 2005) and patients (Tawn and Whitehouse, 2003).

Several of these investigations are worth highlighting. In the Sellafield workers, it was shown that chronic exposures produced approximately six-fold fewer chromosome aberrations per unit dose compared to the acute exposures received by the A-bomb survivors (Tucker et al., 1997a, b). However, these results do provide solid evidence for the accumulation of translocations under conditions of chronic occupational exposure, and also indicate that translocations persist for decades. Chronic radiation exposure from internal irradiation from plutonium in former Rocky Flats workers induced elevated rates of stable chromosome aberrations indicating that FISH-based chromosome analysis can be a reliable method for detecting exposure to internal alpha irradiation (Livingston et al., 2006). In contrast to numerous studies that report the persistence of translocations over time following exposure to low LET radiation, a recent study based on only 6 astronauts reported a decrease in the frequency of translocations over 10–58 months after spaceflight, which included exposure to high-LET radiations (George et al., 2005). The investigators have suggested that space radiation is sufficiently different than terrestrial radiation that some cells with translocations may have become unstable with time following traversal by a high-LET particle.

In a study of thyroid nodularity and cancer among Chernobyl workers from Estonia (Inskip et al., 1997), nodularity showed a non-significant positive association with the proportion of lymphocytes with chromosome translocations. The mean documented population dose was 10.8 cGy, which was substantially lower than expected (Littlefield et al., 1998). This result was subsequently confirmed in an independent study (Jones et al., 2002) which demonstrated the ability to detect a significant increase in translocations as a result of radiation exposure in the presence of two modifying factors, aging and cigarette smoking. Providing dosimetry for such low doses is possible on a population basis as many of these studies show, but it may not be possible to obtain data with sufficient accuracy for individual subjects.

The most notable feature in common among these studies is that all involved retrospective biological dosimetry, which was made possible, or significantly enhanced, by the analysis of translocations identified by chromosome painting. These papers as well as many others reporting on the use of FISH for translocation analyses have made major contributions to our understanding of the long-term risks of exposure to ionizing radiation.

3.3. Use of GPA in epidemiologic studies

Past studies of the atomic bomb survivors have demonstrated a linear relationship between estimated dose and variant cell frequencies (GPA) following acute, high dose, whole-body exposures (Langlois et al., 1987; Kyoizumi et al., 1996, 2005). Exposure to cesium-137 following the Goiania accident revealed excellent linear correlation of GPA with dicentric chromosome aberrations (Straume et al., 1991). In contrast to these studies, exposure to radiation from the Chernobyl accident for 625 Russian workers and 182 controls was not associated with an increase in the GPA assay after adjustment

Table 1
Characteristics of principal dose reconstruction and epidemiologic studies that have used retrospective biodosimetry, grouped by analytic method (EPR, FISH, GPA, TL/OSL) and circumstances of exposure (accident, occupational, medical, and environmental)

Population	Literature references	Type of exposure[a]	Type of radiation	No. of subjects studied	Dose, Gy (mean, range)[b]	Time since exposure (yr)	Comments
EPR: accidents							
Atomic bomb survivors: adult health study	Nakamura et al. (1998b)	Acute	Gamma, neutron	100 teeth	< 0.005 to > 3	40	EPR signal intensity was well correlated with chromosome aberration frequency ($R = 0.87$)
Chernobyl liquidators	Chumak et al. (1999)	Fractionated	Gamma, beta	> 300	0.035–2.220	< 10	Doses in excess of 100 mGy were reconstructed with uncertainty ±40%
Lilo (Georgia) accident victims	Cosset (2002), IAEA (2002)	Protracted, partial body	^{137}Cs, eight other Cs sources with lower activity; ^{60}Co, ^{226}Ra	8	25–30, local doses; 0.1–4.5 by EPR	< 4	Tooth enamel and bone used for EPR
Russian Navy and Chernobyl victims	Sevan'kaev et al. (2005)	Acute	Beta/gamma, neutron	34	0.1–10	10–40	Both persistent stable translocations and EPR spectroscopy signals are suitable with similar efficiencies for retrospective biodosimetry after acute whole-body exposure
EPR: occupational exposures							
Mayak nuclear workers	Romanyukha et al. (2000)	Protracted	Gamma, plutonium	24	0.078–3.45	50	Two independent laboratories evaluated each tooth. Close agreement between official film-badge and official doses for workers after 1961; official doses were higher than EPR doses for earlier workers, suggesting an overestimation of dose for high dose exposed workers
Mayak nuclear workers	Wieser et al. (2006b)	Protracted	Gamma, plutonium	44	5.7	50	Differences in occupational lifetime dose estimates from film badges and from teeth enamel depended on type of film badge and plant. Radiochemical processing plant: dose was0.57 Gy larger than estimated from EPR. Reactor and isotope processing plants: average difference in doses was −4 and 6 mGy, respectively
EPR: environmental exposures							
Public living in Bryansk areas (Russia) exposed to Chernobyl contamination	Skvortsov et al. (2000)	Protracted	Gamma, ^{137}Cs, ^{134}Cs	2970	0.03 ± 0.01 to 0.22 ± 0.09	10–13	Large scale dosimetry investigation of population in order to validate analytical methods of dose reconstruction in support of epidemiological studies
Public near the Semipalatinsk Nuclear Test Site	Ivannikov et al. (2002)	Protracted	Gamma (fallout), ^{90}Sr, ^{137}Cs, ^{239,240}Pu	26	< 0.25	40	Increased dose values were significantly larger than those obtained for a group of younger residents from heavily exposed territories and residents not exposed to radioactive fallout
Public near the Semipalatinsk Nuclear Test Site	Romanyukha et al. (2002a)	Protracted	Gamma (fallout), ^{90}Sr, ^{137}Cs, ^{239,240}Pu	9 (Kainar) 23 (Znamenka)	0.39 ± 0.070 0.095 ± 0.040	35	Long-term storage of teeth up to 35 yrs had no significant effect on EPR dose reconstruction. Kainar teeth showed a strong radiation-induced signal, and mean dose for Znamenka was consistent with background exposure for 50–65 yrs of age
Public near the Semipalatinsk Nuclear Test Site	Ivannikov et al. (2006)	Protracted	Gamma (fallout)	39	From background to 0.44 ± 0.11	> 50	Dosimetry investigation of population in order to validate analytical methods of individual dose reconstruction in support of epidemiological studies

Table 1 *Continued*

Population	Literature references	Type of exposure[a]	Type of radiation	No. of subjects studied	Dose, Gy (mean, range)[b]	Time since exposure (yr)	Comments
Public in nine villages near the Semipalatinsk Nuclear Test Site	Sholom et al. (2007)	Protracted	Gamma (fallout)	102	Mean values (±1 SEM): Bolshaya Vladimirovka: 0.98 ± 0.22 Dolon: 2.2 ± 1.3 Kainar: 0.69 ± 0.41 Kanonerka: 2.3 ± 1.7 Karaul: 1.3 ± 0.28 Korosteli: 0.71 ± 0.18 Novopokrovka: 0.63 ± 0.17 Sarzhal: 1.6 ± 0.86 Semipalatinsk: 0.25 ± 0.20	> 50	Dosimetry investigation of population in support of epidemiological studies. Data presented are for lateral teeth
Public near the Semipalatinsk Nuclear Test Site	Stepanenko et al. (2006a)	Protracted	Gamma (fallout)	16	0.14 ± 0.039, Mean value, Dolon village, Kazakhstan	> 50	Intercomparison of EPR method with analytical calculations. Comparison of EPR dosimetry data with calculated dose in the air provide the value of "shielding and behavior" dose reduction factor for inhabitants in Dolon to be 0.28 ± 0.068
Public exposed to Techa River, (Urals, Russia) contamination	Romanyukha et al. (2001)	Protracted, internal	Gamma, ^{90}Sr, ^{137}Cs	35	0.1 ± 0.08 to 15.0 ± 1.0	50	No dependence of dose in tooth enamel on distance from site of release for residents downstream from Muslyumovo who received internal exposures from consumption of Techa River water. Residents born 1946–1949 have high doses detected in enamel of teeth due to permanent teeth in developmental stages
FISH: accidents							
Atomic bomb survivors: adult health study	Kodama et al. (2001)	Acute	Gamma, neutron	3042	< 0.005 to > 3 0.9, Hiroshima 0.83, Nagasaki	23–45	A highly significant and non-linear dose response with a modest degree of upward curvature for dose up to 1.5 Gy, with some leveling off at higher doses. Dose response significantly steeper in Hiroshima than Nagasaki. Type of shielding modified the dose response
Chernobyl liquidators	Littlefield et al. (1998)	Fractionated	Gamma, beta	118	0.10	9	No correlation between translocation frequencies and recorded measurements of physical doses. Translocation frequency was lower in exposed workers compared to controls
Chernobyl liquidators	Moore and Tucker (1999)	Fractionated	Gamma, beta	192	0.25 (0.02–2.7)	5–10	Increased frequency of stable chromosome aberrations is a significant qualitative biodosimeter
Chernobyl liquidators	Jones et al. (2002)	Fractionated	Gamma, beta	341	0.09	6–13	Radiation exposure at Chernobyl was a statistically significant factor for translocation frequency
Chernobyl reactor crew	Sevan'kaev et al. (2005)	Acute	Gamma, beta	10	1.0–10.0	10–13	Good agreement for those victims with dose estimates up to 3 Gy. Translocation frequencies were lower than expected between 3 and 10 Gy

Goiania accident victims	Straume et al. (1991)	Protracted	Gamma and beta from ^{137}Cs source	3	0–7	1	Intercomparison of FISH and GPA. Dose estimation based on translocations underestimate doses at time of accident
Goiania accident victims	Natarajan et al. (1998)	Protracted	Gamma and beta from ^{137}Cs source	24	0.1–0.9	5–8	Translocation frequencies were lower than dicentric frequencies, especially at >1 Gy. Multiple samples collected per subject over time
Goiania accident victims	Camparoto et al. (2003)	Acute	Gamma and beta from ^{137}Cs source	10	0.3–1.9	10	Increase in translocations only for exposures <0.5 Gy, whereas doses >0.5 Gy are underestimated by translocation frequency
Industrial accident victims	Sevan'kaev et al. (2002)	Fractionated	Gamma from ^{192}Ir source	3	1.0–3.0	0.1–1.0	Intercomparison of physics calculations, the levels of blood neutrophils, ESR and FISH; all showed good agreement
Russian Navy	Sevan'kaev et al. (2004)	Acute	Gamma, beta, neutron	24	0.1–4.0	16–40	Intercomparison of FISH, ESR and early blood counts. Good correlation between translocation frequencies and recorded measurements of physical doses
FISH: medical exposures							
Cancer patients	Tawn and Whitehouse (2003)	Fractionated, partial body	X-ray, gamma	8	40–80	5	G-banding; persistent increase in translocations over time
FISH: occupational exposures							
Astronauts	George et al. (2005)	Protracted	Space radiation, high-LET	6	Not given	Pre-flight and 5 to 58 months post-flight	Frequency of total exchanges (mainly translocations) decreased after flight to pre-flight baseline levels for 5 of 6 subjects
Interventional radiologists	Montoro et al. (2005)	Scattered, non-uniform	X-rays	9	0.069 ± 0.025	8–28	Doses estimated by translocations were 4-times larger than the physical (badge) doses
Mayak nuclear workers	Salassidis et al. (1998)	Protracted, internal	Gamma, plutonium	75	0.02–9.91 Gy gamma and 0.26–18.5 kBq-plutonium	35–40	Translocation frequencies showed a significant dependence on gamma doses. Plutonium uptake had no substantial influence on translocation frequency. Individual dose estimates based on FISH were lower than registered doses
Mayak nuclear workers	Burak et al. (2001)	Protracted, internal	Gamma, plutonium	27	0–8.5 gamma; 0–16.65 kBq plutonium	35–40	Translocation frequencies were related to gamma but not plutonium doses. Stable aberration frequency increased 0.7% per Gy
Mayak nuclear workers	Bauchinger et al. (2001)	Protracted, internal	Gamma, plutonium, neutron	69	0.012–6.1	40	Translocation frequencies were highly variable among individuals and were lower than predicted by in vitro calibration curves, especially at the higher dose levels
Medical radiation workers	Verdorfer et al. (2001)	Scattered, non-uniform	X-rays	56 (30 radiology, 6 physicists, 20 nuclear medicine)	<0.015 Sv	6–12	Incidence of aberrations (mostly translocations) in individuals working in radiology did not differ from control subjects. Broad inter-individual variation of aberrations
Sellafield nuclear workers	Tucker (1997b)	Protracted	Gamma	81	$\leqslant 0.050$ ($n=23$), 0.17–1.1 ($n=58$)	45	Significant positive dose response with mean stable aberration frequency. Slope for dose response for stable aberrations is 0.79 ± 0.22 aberrations per 100 cells per Gy
Sellafield nuclear workers	Tawn et al. (2000)	Protracted	Gamma	61	>0.50	45	G-banding: significant positive dose response for stable chromosome aberrations. Parallel analysis to Tucker et al. (1997a)
Sellafield nuclear workers	Tawn et al. (2004)	Protracted	Gamma	295 retired workers	<0.050 ($n=95$), 0.050–0.499 ($n=108$), >0.5 ($n=91$)	45	External dose and age were significantly associated with translocation frequency, but no effect for smoking status. Slope $=0.017$ translocations per cell per year of age ($p=0.024$), and 1.11 translocations per cell per Sv

Table 1 *Continued*

Population	Literature references	Type of exposure[a]	Type of radiation	No. of subjects studied	Dose, Gy (mean, range)[b]	Time since exposure (yr)	Comments
Sellafield nuclear workers	Tawn et al. (2006)	Protracted	Plutonium, internal, external	34 retired workers	0.556 (0.04–1.4) internal; 0.156 (0.6–0.55) external	20	Simple translocation frequency = $17.6 \pm 1.96 \times 10^3$ per genome equivalent. Significantly increased compared to unirradiated control group and group with similar gamma ray external exposure. Cytogenetic analysis can contribute to validation of internal plutonium
Rocky flats workers	Livingston et al. (2006)	Protracted	Plutonium, internal, external	30 17	High dose group: 0.28 Sv external (0.010–0.73)+ 0.168 Sv internal (0.029–20.9); Low dose group: 0.022 Sv external (0.010–0.076)+ 0.0 internal	10–50	Frequency of total translocations was correlated with internal, but not external, dose
FISH: environmental exposures							
Istanbul, Turkey accident victims	Gunalp et al. (2002), IAEA (2002)	Protracted, partial body	Gamma from ^{60}C0 source	5	2.7–3.9	1–2	ARS in 10 adults; dose estimates by translocations were 20% higher than those by dicentrics
Public in Marshall Islands	Lisco and Conard (1967)	Protracted	Gamma (fallout)	43	1.75 ($n = 30$), 0.7 ($n = 13$)	10	Exchange type chromosome aberrations were found only in exposed persons and not controls (classical cytogenetics)
Public near the Semipalatinsk Nuclear Test Site	Stephan et al. (2001)	Protracted, internal	Gamma (fallout), ^{90}Sr, ^{137}Cs, ^{239,240}Pu	10	3	50	Translocation frequency of subjects irradiated in childhood did not differ from controls. Calculated physical doses are too high
Public near the Semipalatinsk Nuclear Test Site	Salomaa et al. (2002)	Protracted, internal	Gamma (fallout), ^{90}Sr, ^{137}Cs, ^{239,240}Pu	59	< 0.5	50	Translocation frequencies in exposed (both older and younger generation) did not differ from controls. These data do not confirm previous physically reconstructed effective doses of > 1 up to 4.5 Gy
Public near the Semipalatinsk Nuclear Test Site	Chaizhunusova et al. (2006)	Protracted, internal	Gamma (fallout), ^{90}Sr, ^{137}Cs, ^{239,240}Pu	10 (Dolon) 5 (Chekoman)	0.18 Not detectable	50	Translocations were 1.6 ± 0.2 for whole genome equivalent for Dolon and 0.6 ± 0.18 for Chekoman, consistent with greater radiation exposure in Dolon
Public in Taiwan exposed to ^{60}Co in building materials	Chen et al. (2000)	Protracted	Gamma from ^{60}Co source	56	0.19–3.4	16	Translocation frequency was 5-times higher in exposed residents ofcontaminated buildings compared to controls
Public in Taiwan exposed to ^{60}Co in building	Hsieh et al. (2001)	Protracted	Gamma from ^{60}Co	10	0.052–0.990	3–7	Good correlation between physical measurement-based and doses estimated from translocations
Public exposed to Techa River, (Urals, Russia) contamination	Bauchinger et al. (1998)	Protracted, internal	Gamma, ^{90}Sr, ^{137}Cs	73	0.4	40	Significantly elevated mean frequency of translocations in study group compared to controls, yielding a collective dose estimate of 0.24 Gy

GPA: accidents							
Atomic bomb survivors: life span study	Langlois et al. (1987)	Acute	Gamma, neutron	43	0.14–8.8	40	Significant positive association of heterozygous (but not homozygous) variant frequencies (VFs) with dose; minimum detectable dose was 0.24 Gy
Atomic bomb survivors: life span study	Kyoizumi et al. (1996)	Acute	Gamma, neutron	1226	$\geqslant$0.01	40	Mutant frequency increased with age at testing and no. of cigarettes smoked. The minimum dose for detecting a significant increase in mutant frequency was 0.24 Sv (95% CI: 0.041–0.51)
Atomic bomb survivors: life span study	Kyoizumi et al. (2005)	Acute	Gamma, neutron	1723	$\geqslant$0.004	40–50	Steeper dose response for cancer vs. cancer-free patients in Hiroshima; no difference in Nagasaki
Chernobyl liquidators	Bigbee et al. (1996)	Fractionated	Gamma, beta	453	0.011 Estonia	9	No significant differences in frequency of VFs in three groups compared with controls. Average dose for all 782 workers was 0.04–0.08 Gy based on GPA assay
				281	0.096 Latvia		
				48	0.16 Lithuania		
Chernobyl liquidators	Moore and Tucker (1997)	Fractionated	Gamma, beta	192	0.09	5–10	GPA variant cells did not differ between exposed and control population, adjusted for age and smoking
Chernobyl liquidators	Jones et al. (2002)	Fractionated	Gamma, beta	370	0.09–0.20	6–13	Radiation exposure did not affect GPA variant frequencies
Goiania accident victims	Straume et al. (1991)	Protracted	Gamma and beta from ^{137}Cs source	5	0–7	1	Excellent linear correlation between GPA and dicentrics
GPA: occupational exposures							
Hospital radiation workers and nuclear power plant workers	Ha et al. (2002)	Protracted	Gamma, X-ray	32 (hospital), 144 (power plant)	0.0092(0–0.068) (hospital), 0.021 (0–0.12) (power plant)	1–20	Significant dose responses found
Sellafield nuclear workers	Tucker et al. (1997b)	Protracted	Gamma	27	0.0088–0.867	45	No significant increase in VFs with dose
Sellafield nuclear workers	Tawn et al. (2003)	Protracted	Gamma	151	0.16 (0–0.50)	45	GPA is insufficiently sensitive to be used for low-dose chronic exposure
				110	1.6 (0.53–5.0)	45	No correlation with dose
				32	7.4 (5.00–16.56)	45	
GPA: environmental exposures							
Public near the Semipalatinsk nuclear test site	Lindholm et al. (2004)	Protracted	Gamma (fallout)	113	0.2–1.0	43–50	VFs (ØN) slightly elevated in exposed subjects compared to controls living in a non-contaminated area, but no increase in NN variant frequencies
GPA: medical exposures							
Medical patients administered Thorotrast	Akiyama et al. (1995)	Protracted	Alpha, internal	21	Not given	45–50	VFs not increased with increasing internal dose from thorium
TL and OSL: environmental exposures							
Atomic bomb exposures	Ichikawa et al. (1996)	Acute	Gamma, neutron	NA[c]		> 20	Samples from Hiroshima and Nagasaki
Atomic bomb exposures	Ichikawa et al. (1987)	Acute	Gamma, neutron	NA		> 40	Samples from Hiroshima from five buildings located at distances between 1.27 and 1.46 km from the hypocenter
Atomic bomb exposures	Nagatomo et al. (1988)	Acute	Gamma, neutron	NA		> 40	Samples from Hiroshima from five buildings located at distances between 1.27 and 2.05 km from the hypocenter
Atomic bomb exposures	Hoshi et al. (1989)	Acute	Gamma, neutron	NA		> 45	Samples from Hiroshima from five buildings located at distances between 1.91 and 2.05 km from the hypocenter

Table 1 *Continued*

Population	Literature references	Type of exposure[a]	Type of radiation	No. of subjects studied	Dose, Gy (mean, range)[b]	Time since exposure (yr)	Comments
Atomic bomb exposures	Nagatomo et al. (1991)	Acute	Gamma, neutron	NA	0.1 (ceramic samples)	> 40	Discrepancy between measurements from Hiroshima and DS86 doses (later resolved, see Young and Kerr, 2005)
Public in Bryansk areas (Russia) exposed to Chernobyl contamination	Bailiff et al. (2005)	Protracted	Gamma, ^{137}Cs, ^{134}Cs	NA	0.051 ± 0.019 to 0.179 ± 0.033	12–13	Dose to quartz in brick, converted to dose in air at reference location. Methodology developed to evaluate cumulative absorbed dose in brick of less than 20 mGy
Public exposed to Chernobyl contamination	Bailiff et al. (2004a)	Protracted	Gamma	NA	0.140 ± 0.005 to 0.85 ± 0.04	15	Dose to quartz in brick, converted to dose in air at reference location. Comparison of luminescence and modeling estimates of dose in two highly contaminated settlements
Public exposed to Nevada Test Site fallout	Haskell et al. (1994)	Protracted	Gamma (fallout)	NA	0.038 ± 0.15	> 35	Dose to quartz crystals in bricks. Independent measurement of fallout radiation doses to selected communities in Utah
Public near the Semipalatinsk Nuclear Test Site	Bailiff et al. (2004b)	Protracted	Gamma (fallout)	NA	0.182 ± 0.038 (Dolon)	> 50	Dose to quartz crystals in bricks, converted to dose in air at reference location. Samples include former church in Dolon village. Interlaboratory comparison yielded agreement within ±10%
Public near the Semipalatinsk Nuclear Test Site	Göksu et al. (2006)	Protracted	Gamma (fallout)	NA	0.204 ± 0.038	> 50	Dose to quartz crystals in bricks. Samples from buildings in Dolon village. Part of international intercomparison of TL/OSL. No systematic difference found between TL and OSL, 4 labs from different countries found to be within ±10%
Public near the Semipalatinsk Nuclear Test Site	Gordeev et al. (2006)	Protracted	Gamma (fallout)	NA	0.48–1.4 (Dolon), 0.24 (Kanonerka)	> 50	Intercomparison of various methods
Public near the Semipalatinsk Nuclear Test Site	Sato et al. (2006)	Protracted	Gamma (fallout)	NA	0.249 ± 0.045	> 50	Dose to quartz crystals in bricks from former churches and school in Dolon village. Part of international intercomparison (5 labs)
Public near the Semipalatinsk Nuclear Test Site	Stepanenko et al. (2006c)	Protracted	Gamma (fallout)	NA	0.460 ± 0.092	> 50	Dose to air recalculated from measurements in bricks from buildings in Dolon village. Dose in air estimated by luminescence data comparable with analytical calculations of dose in air: 0.460 ± 0.092 Gy (luminescence) vs. 0.645 ± 0.070 Gy (calculation)
Public near the Semipalatinsk Nuclear Test Site	Takada et al. (1999)	Protracted	Gamma (fallout)	NA	Background to 1.0	> 50	Estimates in Semipalatinsk very high compared with the previously reported values based on military data
Public exposed to Techa River, (Urals, Russia) contamination	Göksu et al. (2002a)	Protracted	Gamma (^{137}Cs release)	NA	0.15–0.2	> 50	Interlaboratory comparison of determinations of dose to quartz in brick from the lower Techa river valley settlement of Muslymovo (4 labs). Agreement within ±21%
Public exposed to Techa River, (Urals, Russia) contamination	Tarenenko et al. (2003)	Protracted	Gamma (^{137}Cs release)	NA	~ 3–4 Gy	> 50	Dose to quartz in brick, using luminescence techniques, converted to dose in air and compared with modeling estimates of dose for a building in the upper Techa riverside settlement of Metlino
Tammiku, Estonia accident victims	IAEA (1998)	Protracted	Gamma (^{137}Cs source)	NA	0.1–25	> 2	Use of luminescence to determine the absorbed dose to ceramics taken from various locations in an occupied house to identify probable storage (~ 1 month) location of a stolen ^{137}Cs source (2 ± 0.4 TBq)

[a]Assume external whole-body exposure unless otherwise noted.
[b]NA is not applicable.
[c]Doses are based on physical measurements, biodosimetry or both.

for smoking and age (Moore et al., 1997; Jones et al., 2002). The GPA assay was also applied to 734 Chernobyl clean-up workers and 51 controls from the Baltic countries to validate dose records for the workers based on prior physical measurements (median dose, 9.5 cGy). Again, no differences in variant frequencies of GPA between exposed and non-exposed clean-up workers were detected, most likely due to the low doses of radiation received by the workers (Bigbee et al., 1996). To evaluate the utility of GPA as a biodosimeter of radiation doses accumulated over a long period of time, the GPA assay was applied to 36 radiation workers at the Sellafield Nuclear Facility who had received > 50 mGy cumulative dose based on previously recorded doses. No correlation was evident between variant frequency measured by GPA and radiation dose (Tucker et al., 1997b; Tawn et al., 2003). GPA ØN variant frequencies, but not NN V_f, were only slightly elevated among the population living near the Semipalatinsk nuclear test site, but were not significantly greater compared with matched controls living in a non-contaminated area (Lindholm et al., 2004). These results suggested that the GPA assay was not a reliable predictor of moderate or low-dose radiation exposure accumulated over a long period of time. Moreover, Lindholm et al. (2004) point out that the long-term stability and persistence of radiation-induced GPA erythrocyte variants is unclear (Lindholm et al., 2004). A significant dose response of variant frequencies related to cumulative dose among hospital workers was noted in one study, but the results were likely influenced by a few persons with high cumulative doses (Ha et al., 2002).

3.4. Use of TL/OSL in epidemiologic studies

TL and OSL have been used in a limited number of epidemiologic studies including many of the major dose reconstructions carried out to date, e.g., for A-bomb survivors (Young and Kerr, 2005; Ichikawa et al., 1996, 1987; Nagatomo et al., 1988, 1991; Hoshi et al., 1989), Nevada test site exposures (Haskell et al., 1994), for the Chernobyl accident (Stepanenko et al., 2003; Bailiff et al., 2004a, 2005) and more recently, for Semipalatinsk nuclear test site exposures (Bailiff et al., 2004b; Stepanenko et al., 2006a–c. Göksu et al., 2006; Sato et al., 2006; Simon et al., 2005; Takada et al., 1999). In all cases, building materials were evaluated for TL or OSL signals.

An international intercomparison of retrospective TL/OSL dosimetry, performed in 2006 using four brick samples collected from three buildings in Dolon village (Kazakhstan), located in the vicinity of the Semipalatinsk nuclear test site (Sato et al., 2006; Stepanenko et al., 2006a, c; Simon et al., 2005; Göksu et al., 2006), obtained results that were in good agreement among the six participating labs (Hoshi et al., 2006).

At the time of this report, there are no published reports on the application of TL or OSL to biologic samples as part of an epidemiologic study.

4. Summary and conclusions

This committee has evaluated the primary methods of biodosimetry that have been used in retrospective dose estimation over the last two decades, though no pretense is made that every technique has been considered. Historically, FISH has been the most widely applied biodosimetry technique in epidemiologic studies and results of those investigations provide evidence that dose-related translocations persist for decades. At the molecular level, free radical interactions may cause DNA lesions, a proportion of which fail to repair or mis-repair. These rearrangements can be visualized at the cellular level as chromosomal aberrations. Such alterations, particularly, the so-called stable types (translocations that can pass unimpeded through cell divisions), are recognized to be a very early step in the processes leading to cancer. As FISH is particularly suited to the detection of persisting translocations, this method has been widely applied as a retrospective biodosimetry technique in epidemiological studies, and is considered the most relevant metric of carcinogenesis of any of the methods discussed. Despite these strengths, rates of translocations are known to vary significantly among individuals, to vary with increasing age and possibly with other exogenous conditions, e.g., smoking or exposure to environmental mutagens. This variation suggests, as numerous authors have, that FISH is most amenable to estimating group average dose. FISH is also a very expensive technique, and cost is almost always a limiting factor in applying it. EPR tooth dosimetry has been successfully used to validate dose models of acute and chronic radiation exposure and in some cases, to estimate individual doses. Because the EPR signal is generally stable with time (though it can be confounded by UV radiation and medical exposure) and because inter-individual variability is relatively low, it remains as possibly the strongest technique for individual dose assessment. Until recently, one great disadvantage of EPR was the necessity of obtaining extracted teeth. The promise of an in vivo measurement capability with a detection limit low enough to be of value in epidemiologic studies (say 0.1 Gy) makes EPR a more attractive technique in the future. Somatic cell assays, e.g., GPA, have been correlated with physically based radiation dose following high-dose, acute exposures, but not low-dose, chronic exposures. A major limitation of the GPA technique is that only 50% of the general population is eligible for that assay. Another limitation for GPA (as well as for FISH) is the inter-individual variability. As explained, both of these techniques can be used to estimate the level of past radiation exposure to a population, whereas EPR can potentially provide individual dose estimates of past exposure. TL and OSL, as noted earlier, may be considered as a biodosimetry technique if applied to tooth enamel or bones. When used as a complementary method with building materials and artifacts, it has the advantage that biological variability is not present. It is important to note that when applied to such materials its purpose is not related to an assessment of the dose to individuals. However, when applied to buildings in settlements, determinations of cumulative gamma dose in air can be used to provide benchmark values in calculations to reconstruct doses to populations.

The focus of this discussion on EPR, FISH, GPA and TL/OSL agrees with the evaluation of ICRU (2002) that these four techniques are the most suitable ones for time periods

greater than a few months after exposure and that other measurement-based methods presently available are primarily suitable for short times after exposure (ICRU, Table 6.1). ICRU also considered the laboratory effort required per measurement as measured in person-days per analysis. It concluded that GPA required the least time (~ 0.2 person-day per measurement), EPR considerably more (~ 1 person-day per measurement) and similar, but longer times for luminescence and FISH analyses (2–2.5 person-days per measurement). These estimates have not likely changed to any great extent since that publication, though the number of samples that can be analyzed per unit time (throughput) in any specific laboratory can vary considerably depending on organization of the laboratory and whether strategies have been implemented for preparation steps of many samples in parallel.

Table 2 is provided as a means to summarize these and other characteristics of the techniques considered here. Several points can be concluded from the information presented there. For example, the minimum detectable dose for EPR (~ 0.03 Gy) and TL/OSL (~ 0.01 Gy, using building materials, not tooth enamel) are roughly comparable, with GPA and FISH being about one order of magnitude, or more, greater (~ 0.3–0.5 Gy for FISH). The range of minimum detectable dose for FISH is based on in vitro dose–response curves and available data on unexposed subjects leading to estimates of ~ 0.3 Gy for persons less than 40 years of age to 0.5 Gy for individuals from 40 to 50 years of age (Pressl et al., 2000; Moquet et al., 2000; Edwards, 2000). Although there is considerable uncertainty in the estimation of individual doses by the FISH technique, cytogenetic dosimetry can potentially be improved for groups of subjects and with the scoring of more cells. Thus, it may be possible to detect doses as low as 0.18–0.25 Gy (Edwards, 1997; Darroudi and Natarajan, 2000).

The four techniques (FISH, EPR, TL/OSL) appear to have stable signals for many decades making them potentially useful at long times after exposure. At this time, laboratory costs differ considerably with FISH generally the most expensive on a per sample basis, though the equipment needed for EPR and TL/OSL is probably greater when considered as an initial investment. Sensitivity (detection limits), ability to estimate doses to individuals as opposed to groups, low cost to implement, and resistance to confounding factors are four important determinants of the usefulness of biodosimetric techniques. Certainly, any new techniques that are developed need to address these needs.

One capability that is not yet well developed is for biodosimetric techniques to quantify internal exposures to radionuclides. There have been some possibilities demonstrated, but not all with equal success or development. For example, it may be possible to discern ^{90}Sr exposure using a photostimulable phosphor imaging detector (Romanyukha et al., 2002b) and dose to bone marrow from internal plutonium exposure using mFISH (Hande et al., 2003) has been demonstrated. In addition, FISH has been shown to work well for a limited number of incorporated radionuclides e.g., for ^{137}Cs, where it was used following the Goiania accident (Camparoto et al., 2003) and for tritiated water, where it was used 6 and 11 years after an industrial accident (Lloyd et al., 1998). In both of those cases, the body received generally uniform exposure due to the tendency of those specific nuclides to distribute themselves uniformly. In general, however, the methods amenable to evaluating the often more common and sometimes more important historical exposures, e.g., ingestion or inhalation or short-lived radioiodines or most other fission products, do not exist. The need to evaluate past internal doses transcends needs of epidemiologic studies as there are also national defense needs for such techniques, as well as the need to provide information in radiation exposure litigation.

Epidemiologic studies of radiation related cancer usually focus on the cancer risk for specific organs or tissues of the body, except those designed as mortality studies or studies of overall cancer incidence, usually focus on the cancer risk for specific organs or tissues of the body. To quantify the risk to a specific organ, relatively precise doses estimates to that organ are needed for all individuals in the cohort and there should be minimal bias in estimated dose with exposure status. As discussed here, the three most useful retrospective dosimetry techniques, i.e., FISH, EPR, and OSL/TL, all have one limitation in common, that is, none truly estimate the radiation absorbed dose to all the tissues/organs of interest and in some cases, do not estimate the actual dose to any organ. Hence, none of these techniques completely satisfy the requirements of epidemiologic investigations to estimate the absorbed dose to all organs of interest. Presently available techniques should be viewed as indicators of a particular metric of radiation exposure or dose, but one that usually requires refinement for use in epidemiologic studies. New techniques that may be developed will hopefully address some of the present weaknesses.

Of the techniques considered, FISH may best reflect the dose as averaged over the body, while EPR reflects, without any argument, absorbed dose in tooth enamel. Both methods likely require that techniques of analytical dosimetry (i.e., model-based methods) be used to estimate dose to the organ(s) of interest. Hence, the precision of the measurement may be of considerably less importance than imagined because extrapolation to other body organs is necessary and that can introduce large uncertainty.

It seems clear that biodosimetry has and should continue to play an important role in long-term health risk studies as well as any circumstances where dose estimation is needed at long times after exposure. Uncertainty of analytical dose estimation has been widely recognized (Hoffman et al., 1997) and generally attributed to lack of knowledge about individual exposure conditions, simplistic assumptions necessary to model radiation transport and environmental transfer and, often, the lack of appropriate model input data or the questionable relevance of available data. The clear and obvious value of biodosimetric techniques, at least in the immediate future, is to help reduce uncertainty in retrospective dose estimation obtained by analytical or model-based estimations. This reduction in uncertainty can either be a result of individual biodosimetric measurements replacing analytical dose estimations or by the use

Table 2
Characteristics of selected biological and physical dosimetry methods useful for retrospective dose assessment and epidemiologic studies of irradiated populations[a]

Characteristic	Method			
	Electron paramagnetic resonance (EPR)	Cytogenetic analysis (FISH)	Glycophorin-A mutation assay (GPA)	Luminescence (TL/OSL)
Radiation type	Gamma, X-rays, beta	Gamma, X-rays, neutrons	Gamma	Gamma, X-rays, beta
Minimum detectable dose	~ 0.03 Gy	0.3–0.5 Gy depending on age and other factors	~ 0.1–0.2 Gy, most useful at $\geqslant 1$ Gy	~ 0.01 Gy for TL and OSL in building materials, 4–6 Gy for OSL in teeth
Time limitation	Up to several decades after exposure, cumulative	Up to several decades after exposure, cumulative	Up to several decades after exposure, cumulative	Up to many decades after exposure
Individual dose assessment	Yes	Yes, but inter-individual variation may be high	Yes, but inter-individual variation is high	Indirectly only (when using building materials), Yes, for teeth
Modifiers of dose response	UV exposure	Age and tobacco smoke	None	Contamination of retrospective signal with natural radioactivity
Application to irradiated populations (whole-body exposures)	A-bomb survivors, radiation workers, Chernobyl clean-up workers, residents near nuclear test sites and nuclear facilities, Naval crew	A-bomb survivors, accident victims, Chernobyl clean-up workers, radiation workers, residents near nuclear test sites and nuclear facilities, medical radiation workers, medical patients, industrial accidents, Naval and air crew	A-bomb survivors, radiation workers, Chernobyl clean-up workers, hospital workers, residents near nuclear test sites	Relevant for locations exposed to fallout or atmospheric deposition, exposures from accidents, etc.
Primary use	Validate radiation exposure models and determine individual cumulative radiation dose	Provide evidence of past radiation exposure level on a population basis	Provide evidence of past radiation exposure level	Provide exposure estimates (or air kerma) at location of buildings inhabited or used by exposed populations
Advantages	Individual dose assessment, low minimum detectable dose	Well characterized dose-response curves	Practical to use in field conditions, small amount of blood required	Low detection limits, samples (except for teeth) are not biologically invasive
Disadvantages	Usually requires teeth for ex vivo measurement, inability to distinguish radiation type (gamma, beta and X-rays) and difficulties in separating UV radiation from ionizing radiation contribution	Inter-individual variability in the background control frequency affects usefulness as an individual biodosimeter	Only 50% of the population is eligible for assay; no in vitro assay	Measurements primarily reflect living and working environments rather than individual
Practical considerations	Reliable, can require considerable laboratory time, moderately expensive	Reliable, requires considerable laboratory time, most expensive of techniques	Not useful for exposures < 1 Gy; inexpensive	Careful sample extraction needed; modeling required to give air kerma, less expensive than cytogenetics and EPR

[a]Adapted and modified from Kleinerman et al. (2006, p. 288).

of biodosimetry in a supportive role to adjust for bias or to corroborate model-based dose estimates.

The analysis here does not suggest that any of these techniques, except possibly GPA, be eliminated from research programs on retrospective dosimetry or from availability in biodefense initiatives. But it seems clear that certain improvements would be extremely valuable, namely reduction in throughput time and cost, low invasiveness to individuals, verifiable precision (obtained through international intercomparison exercises) and an increase in sensitivity (lower detection limits). Radiation epidemiology and other long-term studies, unlike emergency response programs, collect samples many years after exposure and can allow for moderately time-consuming laboratory analyses. And unlike medical triage activities that seek to classify individuals into gross categories of exposure, health risk analyses depend on eliminating misclassification of dose by obtaining the highest precision dose estimates possible for individuals. These arguments suggest that the challenges of retrospective dose estimation for epidemiologic studies are somewhat unique. Future radiation epidemiologic studies, particularly those where model-based estimates of dose are highly uncertain, will undoubtedly benefit from continued improvements in biodosimetry methods.

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Author's note

The opinion expressed in this report represents the collective view of the authors who participated on the Consensus Committee; it is not intended to represent the opinion of any single institution or group of institutions.

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