

# Biodosimetric tools for a fast triage of people accidentally exposed to ionising radiation. Statistical and computational aspects

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**Summary.** Consideration of statistical methodology is essential for the application of cytogenetic and other biodosimetry techniques to triage for mass casualty situations. This is because the requirement for speed and accuracy in biodosimetric triage necessarily introduces greater uncertainties than would be acceptable in day-to-day biodosimetry. Additionally, in a large scale accident type situation, it is expected that a large number of laboratories from around the world will assist and it is likely that each laboratory will use one or more different dosimetry techniques. Thus issues arise regarding combination of results and the associated errors. In this article we discuss the statistical and computational aspects of radiation biodosimetry for triage in a large scale accident-type situation. The current status of statistical analysis techniques is reviewed and suggestions are made for improvements to these methods which will allow first responders to estimate doses quickly and reliably for suspected exposed persons.

*Key words:* radiation dosimetry, data analysis, statistical, radiation accidents, triage.

**Riassunto** (*Metodi biodosimetrici per il triage di persone accidentalmente esposte alle radiazioni ionizzanti. Aspetti statistici e computazionali*). L'utilizzo di metodologie statistiche è essenziale nell'applicazione della citogenetica e di altre tecniche di biodosimetria nel triage in situazioni di ricovero urgente di massa, perché in questo caso il requisito di urgenza e accuratezza introduce inevitabilmente maggiore incertezza di quanto altrimenti accettabile nella biodosimetria ordinaria. Inoltre, in una tipica situazione di incidente su larga scala, è probabile che laboratori di tutto il mondo cooperino, utilizzando ciascuno la propria tecnica dosimetrica. Sorgono pertanto problemi relativi alla combinazione dei risultati e degli errori a questi associati. In questo articolo discutiamo gli aspetti statistici e di calcolo della biodosimetria di radiazione ionizzante per triage in situazioni di incidenti su larga scala. Questo lavoro esamina lo stato attuale delle tecniche di analisi statistica e fornisce suggerimenti per il miglioramento delle metodologie per permettere ai primi soccorritori di stimare in modo rapido ed affidabile le dosi alle quali le vittime potrebbero essere state esposte.

*Parole chiave:* dosimetria, analisi dei dati, statistica, incidenti radiologici, triage.

## INTRODUCTION

One of the biggest challenges for biological dosimetry is the satisfactory conversion of a measured quantity, such as a dicentric yield, into an estimate of dose. The starting point for any such calculation is the correct interpretation of the uncertainties resulting from the experimental methods. This knowledge can then be used to calculate appropriate standard errors and confidence limits. Established methods exist for a number of dosimetric tools. For instance, for the dicentric assay, the IAEA manual [1] describes tried and tested methods of analysis that have evolved over the lifetime of the development of the assay (on the order of thirty years).

Methods of dose estimation in the framework of triage vary slightly from those for traditional dosimetry. In recent years, a consensus for radionuclear accident triage has begun to emerge. In an accident situation, there are potentially a very large number of exposed persons with a wide distribution of doses. The focus of active triage is initially to divide exposed persons into three categories – those with probable low doses, the “worried-well”, for whom no deterministic effects are expected but long term monitoring may be required; those with intermediate doses, for whom medical intervention will be necessary to mitigate the short, medium and long term effects of radiation exposure, and the severely

exposed, for whom immediate medical intervention could mean the difference between life and death. Critically, dose assessment must be both accurate and timely to ensure appropriate medical intervention can be carried out. Thus biodosimetric triage methods must be both fast and reliable.

## ESTIMATING DOSES

### *Routine dosimetry*

In addition to the IAEA manual [1], there are a number of publications which describe the specifics of the cytogenetic methods. Szluinska *et al.* [2], gave a detailed description of methods for calculating statistical uncertainties on cytogenetic data. The authors describe the well known linear-quadratic model for estimating doses from whole body exposure, and then go on to discuss the relative merits of classical *vs* Bayesian methodologies for estimating and presenting uncertainties. Szluinska *et al.* [3] describe in detail statistical approaches for dose estimation in more complex situations, including criticality estimates, partial body exposures and fractionated or protracted exposures.

### *Dose estimation for triage*

A number of factors require consideration for estimating doses in a triage situation. Alexander *et al.* [4] reported on the BiodosEPR 2006 meeting: "Acute dosimetry consensus committee recommendations for biodosimetry in radionuclear incidents". The authors discuss the potential suitability of four cytogenetic techniques: the dicentric assay, the fluorescence in situ hybridization (FISH) assay, the micronucleus (MN) assay and the premature chromosome condensation (PCC) assay, for short timescale dose assessment. The authors concluded that, of the four methods, because of the long culture time required for the dicentric assay, only the MN and PCC assays show any real potential for field based triage. However these methods also require sample preparation times which can be lengthy.

Recently, several new dosimetry techniques have been proposed, including protein biomarker analyses (*e.g.*  $\gamma$ -H2AX) [5], the skin speckle analyses [6] and serum protein assays [7]. These assays are still in development, and have not yet been tested in a triage situation.

All the biodosimetric methods require a calibration curve in order to translate the observed yield of damage in cells into an estimate of radiation dose. Currently, it is customary for each laboratory around the world which carries out cytogenetic biodosimetry to establish and use its own calibration curves for several different qualities and energies of radiation. However, recently, the focus within the community has been much more strongly geared towards networking – with the idea of sharing of the scoring workload for a large scale emergency. For the WHO BioDoseNet network, for example, the possibilities of remote scoring, sharing scanned images

of metaphases using the internet, has been discussed. Additionally, in a large scale accident situation, decisions must be made quickly. Thus it is necessary to define which calibration curve(s) should be used within an emergency plan. Also, in order to have confidence in the results, regular inter and intra-laboratory comparisons should be carried out.

The importance of the method used for calibration curve fitting should also not be underestimated. The Poisson nature of radiation induced chromosome damage means that the more cells scored for each dose point, the smaller the uncertainties associated with that dose point, and the better the fit. Thus it is recommended to use, certainly for lower doses, at least 1000-2000 cells for each point on the calibration curve. The Poisson error combined with the observed linear quadratic nature of the dose effect curve also means that it is essential to have several points between 0 and 1 Gy. A weighted fitting algorithm should be used so that the errors on the individual data points are included in the fit. It is highly desirable that a standardised method of curve fitting be used between laboratories. Two methodologies, the iteratively reweighted least squares and maximum likelihood approaches, have been proposed for curve fitting and both have been shown to be appropriate for fitting cytogenetic dose response curves [8]. Ideally, the fit should be demonstrated to be good, using, for example, the chi-squared test, and the individual calibration coefficients should be shown to be statistically significant.

### *Partial body exposures*

Many situations can be envisaged for which radiation casualties would only have partial exposures to radiation. In this type of situation, even if personal dose meters are available or physical dosimetry methods such as EPR or OSL [9, 10] are carried out, the intrinsic localisation of these dosimeters means that total body exposures may be vastly under- or over-estimated. Methods have been developed to adapt the dicentric assay for detection of partial body exposures. The IAEA manual [1] recommends either the contaminated Poisson method [11] or the Qdr method [12]. Both rely on the distribution of damaged cells in the body compared to the expected Poisson distribution. However it should be noted that it is generally accepted that between approximately 12 and 24 hours are required for circulating lymphocytes to reach equilibrium [1, 13], therefore doses could be underestimated if blood is sampled too early.

Of the other commonly used biodosimetric techniques, the micronucleus assay is not particularly well suited to partial body exposure detection, as micronuclei are well known to exhibit overdispersion [10]. It has also been found that the translocation assay is less suitable for detection of partial body exposures as there is a decrease in the frequency of aberrations detected by FISH and in the number of cells with two or more aberrations [14].

Where skin is exposed, the newly introduced skin speckle assay will give some indication of the extent of partial body exposure. The  $\gamma$ -H2AX assay also has the potential to allow detection of partial body exposures. Work is ongoing in these areas.

Blakely *et al.* introduced a Qpcc method based on the Qdr method [11] which was shown to be very successful in estimating dose for partial body exposures [15]. It has been shown that the PCC assay was much more effective than the dicentric or micronucleus assays in identifying partial body exposures for which only a very small percentage of the blood lymphocytes were shielded [16]. However, for triage, such a level of distinction would not usually be required – only when the percentage of the body shielded is relatively large does the potential for dose underestimation become important.

The dicentric and PCC assays remain the only widely available dosimetry methods which have been shown to be consistently reliable for partial body exposures. PCC analysis is currently expensive, the assay is only implemented in a few laboratories and it can be technically difficult to carry out. The PCC technique is, however, better suited to high doses than any other cytogenetic technique as it bypasses the G2/M checkpoint which blocks progression of heavily damaged cells into mitosis.

## STATISTICAL ANALYSIS

### *Current situation*

Statistical considerations of the data should play an important role in both the planning and execution of triage biodosimetry. For instance, the analysis for the dicentric assay is based on assumptions from the Poisson model. It has long been accepted that for adequate statistical confidence in the results, the dicentric yield and thus the estimated dose, 500-1000 cells must be analysed for each case. However scoring this number of cells takes time, on the order of 1.5-2 days for an experienced scorer using automated metaphase finding techniques.

### *Numbers of cells to analyse*

A recent inter-laboratory comparison [17] has confirmed the suggestion that, using the dicentric assay, only 50 metaphases are required to be scored in order to identify those individuals who will require medical treatment for their exposures [18]. Statistically, using the HPA Co-60 calibration curve [19], scoring 500 cells allows a dose of  $\sim 200$  mGy to be resolved with an accuracy of  $\pm 100$  mGy. Decreasing the number of cells scored to 50 means that the dose which can be shown to be statistically greater than 0 is increased to  $\sim 400$  mGy with standard errors on the order of  $\pm 300$  mGy. It has also been suggested that scoring 20 cells would be sufficient for a triage situation [18], which would again increase the uncertainties associated with the estimated dose. In the case of triage, where the initial focus is to classify exposed persons into one of three categories, a large

amount of uncertainty would probably be acceptable. However, the current limitations regarding numbers of cells that can be scored on a short timescale may soon be overcome by the introduction of automated “dicentric hunting” software which should be able to satisfactorily score large numbers of cells in short time periods. This software is currently being tested [20] and more work will need to be carried out to answer questions regarding the importance of loss of information and overall consistency of dicentric detection.

Additionally, because the partial body dose detection techniques introduced above rely on the distribution of damaged cells, the methods are only reliable when a large number of cells are scored. Using the example above, 1 dicentric in 50 gives a dose estimate of  $\sim 400$  mGy of low LET radiation. However, with these figures, the minimum detectable partial body dose is on the order of  $\sim 2$  Gy, and the errors associated with this estimate and with the calculated percentage of the body exposed would be very large. Thus the dicentric assay partial body techniques in their current format are unsuitable for a triage situation. However, as above, it is hoped that this problem will be overcome with the introduction of the automatic dicentric scoring software, which now allows distributions of dicentrics to be recorded and thus further investigated.

### *Combination of results of different assays*

Another major challenge for cytogenetic triage is in bringing together the results of the different biodosimetric methods used by different laboratories, such as the dicentric, micronucleus and FISH assays, to rapidly form a single judgement regarding the status of each potentially exposed individual. Several authors have looked at the relative merits of the biodosimetry methods [*e.g.* 17, 21]. However, to date, there has been little consideration of the formal statistical requirements for combination of results of different assays.

There are several established statistical analysis methods upon which such decision making might be based, such as method comparison studies and analysis of variance. The success of the amalgamation of the results will, again, depend on the correct interpretation of the results of the individual analyses and on the appropriate assignment of uncertainties in each case. Thus the relative accuracy of each dosimetry method will be required to be assessed before a formal comparison can be carried out.

## CYTOGENETICS DATA ANALYSIS SOFTWARE

### *Current situation*

Automation of data analysis methods in the form of computational programs and software can be of assistance to researchers in the field as these provide a framework for standardisation of analysis methods, which is of use in reporting results and for network-

ing and intercomparison purposes. Additionally, a properly developed and tested system will allow the user to have a large degree of confidence in the results of the analyses, some of which can be mathematically complex. Experience has shown that well designed programs increase the accuracy and speed of analysis in the day to day running of biodosimetry services. In general, analysis of only a very small number of blood samples is carried out at any one time. The approach of using automated analysis would also be of use in a triage situation, where high throughput processing is desirable because speed is of the essence, and the high pressure environment means that it is much more likely that mistakes will be made. Several bespoke statistical analysis tools have been developed, and a number of these are described, in brief, below.

Several programs and routines have been developed which concentrate on yield curve fitting. An R-based routine was produced at the Helmholtz Zentrum Munich (Germany). The program uses maximum likelihood for curve fitting and the routine can be used to fit a linear or linear quadratic fit, and also gives the significance of the individual yield curve coefficients. A routine using Generalised Linear Interactive Modelling (GLIM, [www.nag.co.uk/stats/GDGE\\_soft.asp](http://www.nag.co.uk/stats/GDGE_soft.asp)) was developed at UAB (Universitat Autònoma de Barcelona, Spain); it is used to find the calibration coefficients for linear and linear quadratic chromosome aberration calibration curves. The program uses the iteratively re-weighted least squares method for curve fitting. Triangular structures (covariances) needed for a further dose estimation can also be obtained from GLIM. The MLREG curve fitting tool was developed at the Bundesamt für Strahlenschutz (Germany). MLREG can be used to fit linear or linear-quadratic calibration curves, with or without a constant coefficient. The curve fitting is based on maximum likelihood methodology and, additionally, the significance of each calibration coefficient is given.

In addition to the above, there are several tools that have recently been developed which combine a number of the suggested methods for mathematical and statistical analysis of cytogenetic data. UAB uses a Microsoft Excel based spreadsheet, BIDOSEUAB, for estimating doses and investigating the distribution of aberrations to detect partial body exposure, using the contaminated Poisson method [8]. Similarly, Institut de Radioprotection et de Sûreté Nucléaire (IRSN) in France has developed an integrated excel-based spreadsheet for calibration curve fitting, calculation of doses, investigation of dose fractionation and partial body exposures using both the Qdr and contaminated Poisson methods [11, 12].

Most recently, analysis software for radiation biodosimetry has been moving towards a graphic-user interface based, user friendly, style. The DOSGEN program was produced at CPHR (Cuba); it allows the user to calculate calibration curve coefficients

using the maximum likelihood approach and can be used to investigate Poisson distribution and partial body irradiation. Chromosomal ABerration cALculation Software (CABAS) was developed by Deperas *et al.* [22] to perform calculations of estimated dose from an observed number of aberrations (nominally dicentric or micronuclei). The software uses maximum likelihood methods to fit calibration data to a linear quadratic dose response curve. CABAS can also be used to estimate parameters of partial body exposure using the method proposed by Dolphin [1]; to correct for protracted or fractionated exposures using the G-function [1], and to estimate the odds ratio of zero dose versus a suspected (*e.g.* badge) dose [2]. Dose Estimate is a similar tool to CABAS, which was developed at the Health Protection Agency (UK) [23], however the Dose Estimate software also allows linear curve fitting and has additional tools including for criticality calculations (for combined neutron and gamma exposures), distribution analyses to ensure that the uncertainties associated with dose estimates are correct, as well as tools for calculating the Lucas' formulae for total genome equivalent numbers of cells for the FISH assay, and p-value calculators for commonly used simple statistical analyses such as the Student's t-test and the chi-squared test. Dose estimate currently uses iteratively re-weighted least squares-based curve fitting. Both the CABAS and Dose Estimate programs produce "Case Reports" detailing the results of the analyses carried out in a single session. Both programs have been tested and validated in a number of EU and worldwide cytogenetics laboratories and have been shown to increase the accuracy and speed of analysis in the day to day running of biodosimetry services.

#### *Requirements for triage analysis software*

There are a number of important points to be considered regarding the use of the existing tools and programs in a triage situation. Firstly, speed and accuracy are of high importance, especially in a large-scale accident type situation. As discussed above, the amalgamation of the mathematical and statistical routines in specially designed data analysis programs promotes integrated data analysis. The user-friendly (currently) Windows based presentation of the programs means that the analysis methods are more accessible to a wider audience.

However, when statistical methods are automated, one of the most important points to be considered is that automation necessarily removes from the user a certain degree of control over the chosen methods. For instance, in order to carry out the chi-squared test, it is necessary to understand something of the form of the chi-squared distribution. The p value represents the probability of observing the value of chi-squared given the number of degrees of freedom. It is easy to imagine a situation in which a user might misinterpret the results, perhaps if the incorrect value for degrees of freedom is used, or if, as is common,

the user simply assumes that  $p < 0.05$  gives a significant result. The significance of the result, of course, depends on the null hypothesis. However automating the analysis means that the user does not necessarily have to understand anything of the form of the distribution or the real meaning of the value of  $p$ , and in this way, mistakes might be made. In the routine laboratory situation, a cytogeneticist analysing data will be trained in the analysis methodology and will thus usually have a good understanding of the data analyses that are carried out. Alternatively analyses will be carried out by a trained analyst or statistician. However, in a mass casualty situation, the biology and statistics might be carried out by a first responder who will potentially have had only rudimentary training in the techniques. A related issue was discussed in Szluinska *et al.* [2], due to the fact that it is the norm for 95% confidence limits to be quoted with cytogenetic dose estimates. The authors point out that it is unlikely that a member of the public who has no scientific or mathematical training would understand the real meaning or implications of the confidence limits. Thus it was suggested that the results of cytogenetic dose estimations should be given in terms of an odds ratio approach, considering, for instance, likelihood of the calculated dose compared to zero dose. This gives a much clearer "picture" of the real likelihood of exposure to a concerned member of the public. Thus it is a requirement that a program or software package that is designed to be used in a mass casualty situation must be absolutely "fool-proof", that the statistical analyses to be carried out should consist of standardised methods that are easy to implement, and that the results are transparent enough to be understood by persons with little or no related training.

Finally, it has been mentioned that, for a large scale accident, sharing of scoring would be desirable. In this case, ease of data transfer (*e.g.* high uploading speed) is also desirable. Software developed for use in the field should ultimately be widely available, platform independent, and allow the user to upload results to a secure central database for further analysis and dissemination amongst the laboratories involved.

## CONCLUSIONS AND RECOMMENDATIONS

There are a number of different dosimetry methods that are being considered for use in a triage situation, from the tried and tested dicentric assay to the newly proposed  $\gamma$ -H2AX assay. Apart from the practical aspects of implementing these methods in the field, it is essential that appropriate statistical analyses be carried out in order to give confidence in the estimated doses, and to identify partial body exposures where appropriate. As discussed, initial work has been carried out testing the reliability of the dicentric assay and the required number of cells for a triage situation. Analysis programs such as CABAS and Dose Estimate could

be adapted to account for the increased uncertainties associated with the smaller sample sizes necessary for triage. However statistical analysis methods have not yet been refined for the newly developed tools such as the  $\gamma$ -H2AX assay, where the level of inter-individual variation of baseline yields of foci has not so far been determined with a sufficient level of reliability. Thus, analysis methods will need to be established and tested for use in the triage framework. In any large scale accident situation, it is likely that a number of laboratories will be involved, and each will contribute to the dose assessment using one or more different dosimetry techniques. Efforts should be concentrated on the unification of dose assessment analysis methods, so that the results of the different techniques and analyses can be reliably combined.

Automation of data analysis is desirable to increase speed and accuracy of the analysis and a well designed graphical user interface based system would allow early (first) responders who are not necessarily trained in the appropriate data analysis techniques to undertake analysis and disseminate results in a much shorter timescale. For the existing (established and validated) dosimetry methods several such programs have been developed, but there remains no single, integrated, software program which can be used for analysis of data from all the processes for which the biological dosimetry laboratories round the world are involved. Dose Estimate, CABAS and DOSGEN are the most developed in this respect. Tools also exist for clinical classification of radiation exposed subjects, such as the AFRRRI biodosimetry assessment tool (BAT, found at: [www.affri.usuhs.mil/outreach/pdf/BATbrochure\\_Oct08.pdf](http://www.affri.usuhs.mil/outreach/pdf/BATbrochure_Oct08.pdf)) and first responder assessment tools (FRAT, details can be found at: [www.tswg.gov/subgroups/cbrnc/information-resources/first-responder-radiation-assessment-tools.html?KeepThis=true&TB\\_iframe=true&height=500&width=600](http://www.tswg.gov/subgroups/cbrnc/information-resources/first-responder-radiation-assessment-tools.html?KeepThis=true&TB_iframe=true&height=500&width=600)). Ideally, the methods and algorithms resulting from the above work should be combined with clinical tools such as BAT and FRAT to complement the clinical response. This unified approach will give first responders an integrated collection of tools that can be used for decision making in mass casualty situations.

In order to satisfactorily carry out these tasks, a review of the existing tools and methodologies will be required. The aim of such a review should be to identify the state of the art and any gaps in the knowledge base, before methods to fill these gaps can be developed and tested. This should be in reference to the well developed and defined methodologies for the routine dicentric assay. Consideration should also be made of the number of Bayesian techniques that have recently been developed, mainly for the dicentric assay (*e.g.* [24], to address the problem of detection of small doses), but also for micronuclei (for instance [25], who looked at a Bayesian model for overdispersion).

Following these tasks, the most appropriate statistical method(s) in each case can be combined into a

single package of statistical software. Finally, methods of combining the results of the analyses should be tested and, again, incorporated into the statistical analysis software. Ultimately, this will allow first responders from dosimetry laboratories and the emergency services to quickly and reliably estimate doses for suspected exposed persons, and assign these persons to the appropriate triage categories.

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