Biodosimetry Inter-comparison: FOI and DRDC Ottawa

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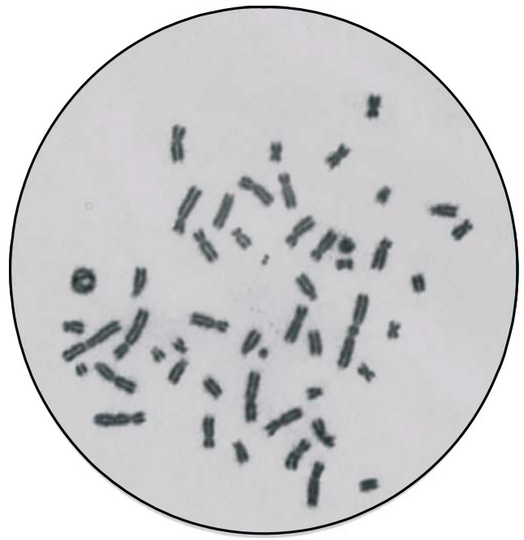

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Abstract

Biodosimetry is used to assess radiation exposure in cases where an over-exposure is suspected and physical dosimetry is absent or in need of validation. Reliable estimate of dose is critical for making life-saving medical decisions, assessing the long-term health consequences, and for reassuring persons with non-significant exposures. The dicentric assay, the current gold standard in biological dosimetry, requires some degree of technical capability and recently published ISO guidelines indicate the need for documenting competence and establishment of quality control programs. Inter-laboratory comparisons are required to document the ability to perform reproducible and accurate assessments.

FOI and DRDC Ottawa have conducted a concise inter-comparison for quality assurance purposes. The exercise involved exchange of previously prepared slides from each laboratory from samples that had been evaluated for each lab's dose response curve. Approximately 100 cells from each slide were evaluated and aberration frequencies reported and compared to the expected frequencies. The results indicated good agreement in analyses for all samples. Comparison of aberration frequencies, rather than dose estimates, further illustrates highly consistent scoring criteria between the two laboratories. The exercise conducted by FOI and DRDC Ottawa provided an efficient means of documenting expertise. Such cooperation further establishes the international biodosimetry network and ensures our readiness for emergency response.

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Internationell Biodosimetri: Jämförelse FOI och DRDC Ottawa

Sammanfattning

Biodosimetri används för att kunna göra en biologisk bedömning av en strålningsexponering i de fall där fysikalisk dosimetri inte är tillgänglig eller behöver valideras. En tillförlitlig dosuppskattning är ofta viktig för att kunna fatta kritiska medicinska beslut, för att kunna bedöma långsiktiga hälsokonsekvenser och för att lugna personer som inte exponerats. Den dicentriska metoden, biodosimetrins gyllene standard, kräver viss teknisk förmåga. Riktlinjer som nyligen publicerats av ISO pekar på behovet att dokumentera kompetens och etablera program för kvalitetskontroll. Jämförelser mellan olika laboratorier krävs för att dokumentera förmågan att göra reproducerbara och korrekta dosbedömningar.

FOI och DRDC Ottawa har genomfört en jämförelse med kvalitetssäkring som avsikt. Övningen innebar att man utbytte objektglas med prover som tidigare utvärderats av respektive lab för dess egen dosresponskurva. Ungefär 100 celler från varje prov utvärderades och aberrationsfrekvensen rapporterades och jämfördes med de tidigare erhållna frekvenserna. Resultaten visade på bra överensstämmelse i alla prov. Att jämföra den faktiska frekvensen av aberrationer istället för att jämföra dosuppskattningar visar på ett tydligare sätt att de båda laboratoriernas bedömningsgrund överensstämmer i hög grad. Den övning som genomförts av FOI och DRDC Ottawa är ett effektivt sätt att dokumentera sitt kunnande. Ett sådant samarbete stärker ytterligare det internationella nätverket inom biodosimetrin och säkerställer vår beredskap för akuta händelser.

Nyckelord

Internationell jämförelse, biodosimetri, dicentrisk metoden

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Introduction

Background

Biodosimetry is the biological assessment of radiation dose in individuals and may be used to assess radiation exposure after an accident or in cases where an over-exposure is suspected and physical dosimetry is absent or in need of validation. A reliable estimate of dose is critical for making life-saving medical decisions, assessing the long-term health consequences, and for reassuring persons with non-significant exposures. Access to biodosimetry capabilities is important today as radiological sources are common in the medical setting, for diagnostics and treatment, as well as in the industrial setting, such as for application in sterilization.

Dicentric Assay

While a great many markers and methods exist for biological radiation dose assessment, the evaluation of dicentric chromosomes, which dates back to the 1960's, has been the most widely applied assay and is the most fully validated method available. Application of the dicentric assay over several decades and in nearly every radiation exposure accident has enabled assay optimization and has documented the merit and the limitations of the method. Today, the conventional dicentric assay has come under ISO standardization and has been incorporated into many radiological protection programs (IAEA 1986, 2001, ISO 2004).

In general, the dicentric assay is conducted by culturing blood lymphocytes, from an individual with a suspected exposure, for 48 hours to obtain metaphase chromosomes. The chromosomes of many metaphases, 500 - 1000 cells, are evaluated under a microscope for specific damage in the form of dicentric chromosomes, which are the result of chromosomal breakage from radiation interactions and subsequent abnormal rejoining. Dicentric chromosomes are the markers of choice for evaluation because they are easily identified, are quite specific to radiation, have low background frequency, and show a reproducible dose response relationship (Bauchinger 1984, Amundson 2001).

Technical Requirements

Biodosimetry laboratories that intend to perform the dicentric assay as a service for actual human evaluations must establish their lab as described in ISO regulations (ISO 2004) in order for results to be considered reliable legally defensible. This includes a number of technical requirements, many of which involve incorporating good laboratory practices (GLP), documenting protocols, and establishing quality control programs. Among the criteria for the establishment of a biodosimetry lab is the development of a dose response curve and documentation of all methods used for creating the curve. The biodosimetry lab at the Swedish Defense Research Agency, FOI, completed and published their dose response curve for gamma radiation in the previous year (Stricklin 2005). The DRDC Ottawa laboratory, in accordance with their established working standard (Segura 2005a), has produced an x-ray dose response curve that was tested and validated through a national inter-comparison field exercise (Segura 2005b).

Other important criteria addressed in the ISO guidelines are the competent evaluation of metaphases, or *scoring*. Coding of slides, establishment of appropriate scoring techniques, and demonstration of scoring expertise are required. Only trained and experienced evaluators may contribute to a biodosimetry evaluation. The documentation of scoring expertise must be demonstrated in ***intra-*** and ***inter- laboratory comparisons***, using established scoring criteria, and with such evaluations in agreement within 20% of the reference value. These measures are quite crucial for reproducible and accurate assessments due to the fact that evaluations are somewhat subjective in nature.

During the development of both FOI and DRDC laboratories, intra-comparisons were conducted and documented. At this point in time, inter-comparisons are needed as further quality assurance and to meet the requirements outlined in the ISO guidelines. In response to these guidelines, DRDC Ottawa organized and participated in a national inter-comparison exercise involving four partnering laboratories. The outcome of this first inter-comparison demonstrated the need for establishing and testing the standard operating procedures and a strict requirement for adherence to these procedures. Canada's DRDC Ottawa and Sweden's FOI biodosimetry laboratories have conducted an initial inter-comparison exercise as part of work within a trilateral agreement between Canada, the Netherlands, and Sweden in the area of Biomarkers of Human Exposure, BioHE. The Netherlands does not currently have a service biodosimetry laboratory, and hence did not participate in the undertaking.

Objectives

FOI and DRDC Ottawa have conducted an initial inter-comparison exercise for the purpose of documenting capabilities, quality assurance for each lab, and to meet requirements outlined by the ISO guidelines for service biodosimetry laboratories. The exercise was also a good learning experience for both laboratories, providing insight on how to conduct further inter-comparisons and identifying considerations for future exercises.

Furthermore, this exercise facilitates communication and exchange in this area of work and research, providing an avenue for future interactions. The exercise also serves to build a relationship that could enable the sharing of samples. Currently, both countries have limited resources with Sweden having only one functional laboratory with biodosimetry capabilities. Therefore, the relationship between DRDC Ottawa and FOI could enable sharing samples and work load in the event of a mass casualty accident in which either of the two country's resources could easily be overwhelmed.

Methods

Exchange of Samples

Each laboratory; FOI and DRDC Ottawa, shipped three mounted and coded slides to the other laboratory; each slide containing differently exposed samples. The slides were extra slides from previously evaluated samples, used for different dose points in the dose response curves for each laboratory. Using slides from the dose response curve enabled the use of camparison samples that previously had a critical number of cells evaluated, so that their recorded frequencies could be considered the expected values.

Evaluation of Samples

Each laboratory agreed to evaluate approximately 100 metaphases from each slide and report the frequency of aberrations observed in each. The frequency of aberrations were to be compared rather than a dose estimate which is traditionally used in such inter-comparison, due to the fact that the dose response curve at FOI and DRDC Ottawa are for different quality radiation and hence have different responses. FOI currently has a ^{137}Cs curve for gamma radiation and DRDC Ottawa has a 200 kVp x-ray curve.

Each of two evaluators from the FOI laboratory examined approximately 100 metaphases from each slide provided by DRDC Ottawa. Images of all of the metaphases obtained were reviewed, with unclear metaphases having been reviewed again under the microscope. A consensus between the two evaluators was reached for the frequency of aberrations reported. The FOI laboratory typically records all aberrations observed but uses only dicentric with accompanying acentric fragments for the final aberration frequency. However, for the comparison, the ring frequency was reported as well.

Slides at DRDC Ottawa were scanned with a Cytovision automated metaphase finder. The number of metaphases identified, the number of scoreable metaphases, and the number of metaphases evaluated were recorded. All aberrations were validated by at least two qualified evaluators before being recorded and the number of dicentrics and rings with accompanying acentrics were reported together with the aberration frequency per cell.

Since the frequency data obtained at FOI includes only dicentric aberrations, only dicentric frequencies were used in the comparison of FOI samples. Likewise, since the frequency data obtained at DRDC Ottawa included dicentrics and rings, both dicentrics and rings were included in the comparison to DRDC Ottawa samples.

For statistical analysis, the frequency expected from each laboratory's dose response curve for each sample was assumed to be the *expected frequency* since a large number of cells had previously been evaluated and fitted in development of the curves. The number of aberrations observed during the inter-comparison exercise was then compared to the number of aberrations expected to be observed in the number of cells evaluated for each, based on the *expected frequencies*. Aberration data should follow a Poisson distribution, which was verified for the data obtained for the dose response curves. Aberration frequencies are listed in Table 1.

Statistical significance between the *observed aberrations*, those obtained during the inter-comparison, and the *expected aberrations*, calculated from the expected frequencies, were determined using one sample inference for the Poisson distribution, small sample test; critical value method, as described in Rosner 1995. The formula for calculating the *p*-values listed in Table 2 is shown below:

$$p = 2 \times \left[\sum_{k=0}^{x} \frac{e^{-\mu_o} (\mu_o)^k}{k!} \right] \qquad \text{for } x < \mu_o$$

$$p = 2 \times \left[1 - \sum_{k=0}^{x-1} \frac{e^{-\mu_o} (\mu_o)^k}{k!} \right] \qquad \text{for } x \geq \mu_o$$

The 95% confidence intervals shown in Table 2 for the observed and expected aberrations were obtained from Poisson tables.

Results and Discussion

Inter-comparison Exercise

The results of the evaluations by both labs are summarized in Table 1. DRDC1 - 3 are the samples provided by DRDC Ottawa to FOI for evaluation. Likewise, FOI 1-3 are the samples provided by FOI to DRDC Ottawa for evaluation. Metaphases refer to the number of metaphases identified during the exercise. FOI only obtained enough metaphases to score approximately 100 cells. DRDC used an automated metaphase finder which identified all metaphases in a predefined area on the slide. NS cells refer to the number of non-scoreable metaphases found among those identified. The numbers of cells analyzed were approximately 100, except in one case, FOI 1, where the sample was more highly exposed, and rendered only 76 metaphases for analysis. In this case, the aberration number was quite high and provided an ample number of aberrations for the comparison.

Table 1. Results from the inter-comparison exercise between FOI and DRDC.

Sample ID	Metaphases	NS cells	Cells analyzed	Normal cells	Dicentrics	Rings	Frequencies Ab / cell IC	Frequencies Ab / cell Curve
DRDC 1	112	13	99	99	0	0	0.00	0.00
DRDC 2	126	21	105	98	6	1	0.07	0.03
DRDC 3	140	40	100	92	9	2	0.11	0.10
FOI 1	129	53	76	32	34	6	0.45	0.39
FOI 2	390	14	100	89	2	0	0.02	0.05
FOI 3	412	10	100	70	17	3	0.17	0.17

The normal cells among those analyzed are listed, followed by the dicentrics and rings observed in the evaluations. The expression, Ab/ cells IC, is the aberration frequency observed during the exercise, and refer to either dicentric frequencies or dicentric plus ring frequencies for the DRDC Ottawa and FOI samples, respectively. Ab/ cell curve are those frequencies obtained from the dose response curves of the respective laboratories.

The results indicated very good agreement between the frequencies obtained by each laboratory for 5 out of 6 samples. The data for the statistical analyses along with the 95% confidence intervals for the observed and expected aberrations and the *p*-value for their comparison are listed in Table 2. Again, the DRDC Ottawa samples compare dicentric and rings, FOI samples compare only dicentric aberrations. Two of the analyses resulted in the same number of observed and expected aberrations. Three others were very similar and did not return significantly different results.

Table 2. Statistical analysis of the inter-comparison data.

Sample ID	Number of cells analyzed	No. aberrations *observed*	No. aberrations *expected*	*p*-value
DRDC 1	99	0 *(0, 3.69)*	0 *(0, 3.69)*	1.00
DRDC 2	105	7 *(2.81, 14.42)*	3 *(0.619, 8.77)*	0.07
DRDC 3	100	11 *(5.49, 19.68)*	10 *(4.8, 18.39)*	0.59
FOI 1	76	34 *(24.38, 48.68)*	30 (20.24, 42.83)	0.98
FOI 2	100	2 *(0.242, 7.22)*	5 *(1.62, 11.67)*	0.25
FOI 3	100	17 *(9.90, 27.22)*	17 *(9.90, 27.22)*	1.00

Only one analysis, DRDC 2 was close to being significantly different at the 95% confidence level based on a *p*-value of 0.07. However, the 95% confidence intervals largely overlap for both values. The frequency obtained by DRDC Ottawa was based on the observation of 16 dicentrics with acentric fragments and 3 rings with acentric fragments in a total of 883 metaphase spreads while FOI reported 6 dicentrics and one ring, each with accompanying acentric fragments in a total of 105 cells. In review of the data from FOI, one aberration could be excluded on the basis of the cell being incomplete with one chromosome missing. One other aberration was not perfectly clear and the metaphase could conservatively be considered non-scoreable. These differences would account for the disparity in observed versus expected frequencies. Furthermore, the sample size was limited in the exercise, and inclusion of another 50 cells could easily have resulted in an observed frequency more in line with that of the expected. It is important to note that the two

laboratories did not select the same spreads for scoring thus the aberration frequencies would be expected to vary to some extent depending on the cells analyzed.

Although one analysis differed slightly in the inter-comparison, the results demonstrated remarkably good agreement between the laboratories. Ideally, an inter-comparison would involve the exchange of blood samples that would be in fact cultured and processed by each laboratory. This method has been used for international inter-comparison exercises such as the exercise on whole and partial body irradiation conducted in cooperation with the IAEA (Lloyd 1987) and the more recent exercise coordinated by Institut de Radioprotection et de Sûreté Nucléare (ISRN) on criticality dosimetry (Roy 2004). Laboratories may have subtle differences in processing and handling of samples that may affect the quality of metaphases provided. Within an individual laboratory, an evaluator becomes accustomed to their own quality of metaphase spreads, and the most reliable analysis can be obtained by a lab's own cultures.

Another preference in the inter-comparison would have been that each laboratory provides dose estimates rather than aberration frequencies for the comparison. This way of comparison reduces the uncertainty associated with individual laboratory variation in scoring of metaphases. A large variation due to inconsistencies in scoring between laboratories was observed in the IAEA exercise (Lloyd 1987). The fact that scoring is somewhat subjective is in part why laboratories must obtain their own dose response curves and coefficients which will compensate for this variation and render reliable dose estimates. Since DRDC Ottawa has an x-ray curve and FOI has a γ-curve, another constrain in the comparison was that the laboratories could not use their individual curves for making dose estimates since different quality radiations yield different responses and hence different curve coefficients. The remarkable agreement in the frequency of aberrations reported indicates that the two laboratories actually have very similar and consistent scoring criteria.

One final consideration in this exercise was the limited number of cells evaluated for each sample. This initial inter-comparison was subject to time and funding constraints by both laboratories, otherwise more thorough analyses could be conducted. Typical biodosimetry estimates for actual evaluations are based on at least 500 cells or observation of 100 aberrations (ISO 2004). In the future, one consideration for this type of limited inter-comparison, i.e. exchange of slides, could be evaluation of fewer slides with evaluation of more metaphase cells for each sample.

Evaluation of Dicentrics versus Dicentrics plus Rings

Considerable uncertainty was identified in the FOI lab when evaluating ring aberrations. This laboratory found it particularly difficult to consistently judge whether a ring was centric or acentric, and therefore excluded those data in development of their dose-response curve in an attempt to minimize uncertainty. However, evaluations of centric rings are very useful in analyses of high doses and in differentiating partial body exposures. One consideration for the FOI lab in the future is to re-evaluate the data recorded on ring chromosomes and attempt to develop more certain scoring criteria for these particular aberrations. While only 3 centric ring aberrations were observed in the exercise with DRDC Ottawa, their evaluations appeared to be consistent with DRDC Ottawa's data.

Evaluation of Uncertain Cells

Another issue encountered in this exercise was the handling of uncertain cells in an evaluation. In the development of the dose response curve at FOI, generally only very high quality metaphases were included in the analyses, and experiments were repeated if for some reason less than optimal spreads were obtained. This is not practical or possible, however, in the real world. A patient sample can not be duplicated if the metaphase spreads obtained are not optimal. A good estimate must be managed with the samples initially obtained. Consequently, the issue of how to deal with uncertain cells arises and was a consideration for one sample, DRDC 3, analyzed by the FOI laboratory. A number of uncertain cells, such as cells where centromeres were difficult to

distinguish clearly, were encountered and two approaches were examined for dealing with these cells. One method adopted a very conservative approach, simply excluding all cells that were not perfectly clear. The other method for evaluation of this sample was to struggle more and make the "best" judgment achievable *if at all possible*. For the sample DRDC 3, the conservative method resulted in observation of only 3 aberrations, while the more aggressive approach, which we reported, resulted in 11 observations compared to the 10 expected.

After reviewing all data in the same fashion, a consistent trend towards underestimation was seen in all of the analyses evaluated with the conservative approach. This bias is likely due to the fact that when a cell containing an aberration is unclear and can not easily be evaluated it is more likely to be considered non-scoreable than a normal cell that is simply non-scoreable. We considered this an important finding since it affected the outcome of the analysis significantly. A more aggressive approach for handling uncertain cells in the future will be implemented in an attempt to prevent this bias. Please note, however, that we do not advocate inclusion of cells that are too uncertain to make a good judgment, more simply that an effort should be made when possible.

Summary

This initial inter-comparison conducted between DRDC Ottawa and FOI demonstrated good agreement between the laboratories and indicated comparable scoring criteria between the labs. The exercise also serves to document the competence and capabilities of each lab as well as fulfill requirements for a service laboratory as outlined by the ISO guidelines (ISO 2004). This documentation could facilitate exchange of samples in an accident scenario where the capacity of an individual laboratory is overwhelmed.

The exercise also afforded a learning opportunity in which a variety of issues were addressed. For example, future exercises could be conducted with fewer samples but a larger number of analyses for each. However, in an event where a large number of samples may need to be analyzed, we have demonstrated that scoring of 100 spreads resulted in good agreement between the laboratories. Previous studies have demonstrated that even analysis of 50 spreads would result in medically relevant information, although a higher threshold of detection would need to be accepted (Lloyd 2000, Voisin 2001). Evaluation of centric ring chromosomes will be re-considered by the FOI laboratory. Finally, a very conservative evaluation may also result in a conservative estimate and a more aggressive approach to evaluating uncertain cells is warranted. This provides more support for ensuring that each laboratory develops and uses their own dose response curves.

We considered this exercise an initial inter-comparison since both laboratories had significant time and funding constraints for conducting the exercise. We hope to participate and conduct further exercises in the future. For example, DRDC Ottawa is organizing a second annual inter-comparison to test the Canadian network of laboratories, with the intent to offer international partners an opportunity to participate. These opportunities for international inter-comparisons will strengthen the global biodosimetry network and ensure its readiness for emergency response.

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References

Amundson SA, Bittner M, Meltzer P, et al. Biological indicators for the identification of ionizing radiation exposure in humans. Expert Rev Mol Diagn 1(2):211-219, 2001.

Bauchinger M. Cytogenetic effects in human lymphocytes as a dosimetry system. In: Eisert WS, Mendelsohn ML eds. *Biological dosimetry: Cytometric approaches to mammalian systems*. Berlin: Springer-Verlag; 15-24, 1984.

International Atomic Energy Agency (IAEA). Biological dosimetry: chromosomal aberration analysis for dose assessment. Technical Report Series, No. 260, Vienna, 1986.

International Atomic Energy Agency (IAEA). Cytogenetic analysis for radiation dose assessment. Technical Report Series, No. 405, Vienna, 2001.

ISO. Radiation protection – Performance criteria for service laboratories performing biological dosimetry by cytogenetic. ISO 19238: 2004.

Lloyd DC, Edwards AA, Prosser JS, et al. A collaborative exercise on cytogenetic dosimetry for simulated whole and partial body accidental irradiation. Mutation Research, 179: 197-208, 1987.

Lloyd DC, Edwards AA, Moquet JE, et al. The role of cytogenetics in early triage of radiation casualties. App Rad Isotopes, 52: 1107-1112, 2000.

Rosner B. Hypothesis testing: one sample inference. One sample inference for the Poisson Distribution, 7.11, p. 237-243. In *Fundamentals of Biostatistics*, 4th Ed. Duxbury Press, Harvard University, 1995.

Roy L, Buard V, Delbos M, et al. International intercomparison for criticality dosimetry: the case of biological dosimetry. Radiat Prot Dosimetry, 110(1-4): 471-476, 2004.

Segura T, Prud'homme-Lalonde L, Thorleifson E, Lachapelle S, Mullins D, Qutob S, and Wilkinson D. DRDC Ottawa Working Standard for Biological Dosimetry. DRDC Ottawa Technical Report (TR 2005-106) July 2005a.

Segura T, Thorleifson E, Prud'homme-Lalonde L, Lachapelle S, Mullins D, Qutob S, and Wilkinson D. Biodosimetry and Biomarkers for Radiological Emergency Response. NATO Proceedings Report - Human Factors and Medicine Panel Research Task Group 099: Radiation Bioeffects and Countermeasures. Bethesda, Maryland, U.S.A. 21-23 June 2005b.

Stricklin D, Arvidsson E, Ulvsand T. Establishment of Biodosimetry at FOI: Dicentric Assay Protocol Development and ^{137}Cs Dose Response Curve. FOI scientific report, FOI-R--1570--SE, February 2005.

Voisin P, Benderitter M, Claraz M, et al. The cytogenetic dosimetry of recent accidental overexposure. Cell Mol Biol, 47(3):557-564, 2001.