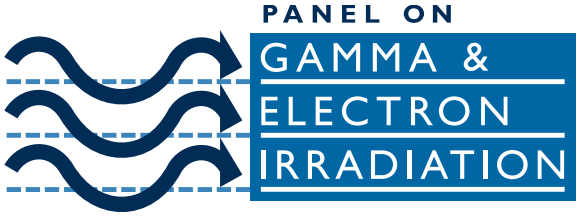
Discussion Paper on Uncertainties in Routine Dosimetry for Gamma and EB Plants



© 1998

DISCUSSION PAPER ON UNCERTAINTIES IN ROUTINE DOSIMETRY FOR GAMMA AND EB PLANTS

Foreword

Measurement uncertainty inherent in the dosimetry for routine processing in industrial irradiation plants is an important, but often poorly understood, topic. The purpose of this document is to provide a framework for understanding the different contributions to the observed variations in routine dosimeter readings and to suggest ways of estimating their magnitude. The document also includes background information on the selection and placement of routine dosimeters.

This document does not set out procedures for the operation of industrial irradiation plants. Such procedures can be found in a number of national and international standards referenced in this document.

DISCUSSION PAPER ON UNCERTAINTIES IN ROUTINE DOSIMETRY FOR GAMMA AND EB PLANTS

1. Introduction

The basic purpose of routine dosimetry in Gamma and EB irradiation plants is set out in The European Standard EN552[1] "Sterilization of medical devices - Validation and routine control of sterilization by irradiation" (sections 6.1.2 and 6.2.2)."*Routine dosimeters shall be used to indicate the dose absorbed by the product*.". The standard then goes on to further set out requirements on:

- **Placement:** "*[Routine dosimeters] shall be placed in the minimum dose position or in a position related to the minimum dose position*"
- **Number:** "*The number of dosimeters used shall be sufficient to verify that the dose absorbed by product falls within specified limits at all times*"
- **Action Limits**: "*Any dosimetric reading indicating a dose outside the specified limits shall be investigated*."

Implicit within these requirements is the necessity to interpret routine dosimetry readings so as to decide when the dose delivered to the product is outside specified limits.

Very similar requirements to the above are also set out in the corresponding international standard ISO11137[2], which also provides a definition of a routine dosimeter :

***"Routine dosimeter**. Dosimeter calibrated against a primary, reference or transfer standard dosimeter and used for routine dosimetry measurements."*

In practice, the doses determined from routine dosimeters exhibit variation. Some of this variation reflects changes in the dose delivered to the product and some reflects uncertainties in the measurement of dose. It is important to understand the causes of variation and to assess their expected magnitude if product release criteria based on routine dosimeter readings are to be meaningful.

The purpose of this document is to provide a framework for understanding the different contributions to the observed variations in routine dosimeter readings and to suggest ways of estimating their magnitude. The document also includes background information on the selection and placement of routine dosimeters.

The present text is not intended to be a guidance document but its production and discussion (by the Panel's Dosimetry and Plant Operators Groups) is intended to be the first stage of a process aimed at producing guidelines for the practice of routine dosimetry. These will include guidance on the definition of acceptance criteria that take into account dosimeter uncertainties.

As a discussion document this text concentrates on the principles and ideas involved. An attempt has been made to minimise mathematical expressions and derivations.

2. Selection and calibration of dosimetry system

The dosimetry system used to monitor irradiation of product must be capable of providing accurate and precise results over the entire dose range of interest. This range will depend on the range of doses for product processed at the irradiation facility and on the position used for routine monitoring.

At gamma irradiation plants the most common practice is to use the same dosimetry system (e.g. Red PMMA) for product dose mapping and routine dosimetry of the sterilization process. However, for dose setting, the range of doses required for a Verification or Incremental dose experiment will frequently be outside the recommended (and calibrated) operating range for the dosimetry system used for routine dosimetry and an alternative system may have to be employed (e.g. Amber PMMA).

At EB irradiation plants the same dosimetry system may be used for product dose mapping and routine dosimetry (e.g. Radiochromic films). Alternatively, in some facilities, different systems are used for dose mapping and routine monitoring (e.g. Radiochromic films for dose mapping and Calorimeters for routine dosimetry).

Further guidance on the selection of dosimetry systems can be found in Annex A of EN552[1], Annex C of ISO Standard 11137[2] and in ASTM Standard E1261[3].

Guidance on the calibration of dosimetry systems has already been given by the Panel on Gamma and Electron Irradiation in "Guidance Notes on the Dosimetric Aspects of Dose-setting Methods" [4]. Further guidance is also given in ASTM Standard E1261[3].

3. Placement of dosimeters for dose mapping and routine control

In order for routine dosimeters to be placed *"in the minimum dose position or in a position related to the minimum dose position"* it will be necessary to carry out some form of dose mapping exercise for each product or product family to be processed. This must be carried out in sufficient detail to identify the maximum and minimum dose positions within the product load in the **irradiation container** (carrier, cart, tray or other container in which products are transported through the irradiator).

Significant dose gradients can occur within irradiated product and this needs to be taken into account when positioning dosimeters for dose mapping. Each case needs to be separately assessed and it is difficult to give detailed guidance. However some basic guidance is given below.

For small low density product units being irradiated by gamma rays, it is usually sufficient to place dosimeters on the outside of the sterile barrier, as there will not be a significant dose gradient on the product unit. Typical examples are product units made up of elements of low atomic number (i.e. non-metallic) that, in addition, do not contain any blocks of material large enough to cause local radiation shielding of adjacent areas.

For product units that contain blocks of material large enough to cause local shielding when being irradiated with gamma rays, and for all product units being irradiated with electrons, it will normally be necessary to place appropriately sized dosimeters on the product itself in order to establish the true maximum and minimum doses. This usually entails dosimeter placement inside the sterile barrier.

In carrying out dose mapping careful attention needs to be given to the size and placement of the dosimeters in order to ensure that the minimum and maximum doses to the product are determined. Dosimeters need to have dimensions such that the dose gradient across the thickness of the dosimeter is not significant. This has implications for the orientation of dosimeters (ensuring the smallest dimension is perpendicular to any significant dose gradient). It should also be noted that in some circumstances dosimeters can themselves generate significant dose gradients. Such a situation should be avoided whereever possible. Care should be taken to ensure that the minimum (and/or maximum) dose is not delivered to positions where there are no dosimeters. Use of dosimeter strips which can subsequently be scanned to give a dose profile may be helpful in this respect (particularly for EB irradiation).

If the routine monitoring position is not at an extreme - maximum or minimum - dose position, then dosimeters are normally placed at the routine monitoring position and irradiated at the same time as the product being dose-mapped. This provides a direct measurement of the ratio between the dose at the maximum or minimum dose position and that at the routine monitoring position.

The considerations involved in the choice of routine monitoring position and the accepted practice is different in the case of gamma and EB irradiators. These are therefore discussed separately below.

3.1. Gamma irradiators

Dose-mapping data should determine the locations of extreme dose for each product presentation and permit the relationship of these positions to the routine monitoring position to be determined. The routine monitoring position will normally be at an easily accessible and standardised position, most often on the outer face of the product packaging. This has the advantage of ease of placement, results in minimum disturbance to the product and reduces the chance of incorrect placing of the dosimeter by the operator. There may, however, be some specific products where dosimeter placement at positions other than this standard position is more appropriate.

In all cases, however, it is important to select a region of the product load in which the dose gradients are low. A routine monitoring position located in a high dose gradient region can lead to significant variations in the recorded dose arising from small variations in dosimeter placement or product loading.

3.2. EB irradiators

As a result of electron range and diffraction effects, significantly higher dose gradients exist in irradiation containers in an EB irradiator compared to those in a gamma irradiator. One consequence of this is that, in general, a larger number of dosimeters need to be employed in dose mapping irradiation containers for EB irradiation compared to gamma irradiation. The electron range and scattering effects also have to be taken into account in considering the choice of location for routine dosimeters. In particular dose gradients on the surface of the product (the favoured routine monitoring position in gamma irradiators) can cause significant problems for routine dosimetry. Slight changes in the positioning of a dosimeter on the surface of product and/or small changes in the arrangement of product within its outer package can cause significant changes to the dose recorded by routine dosimeters under identical processing conditions. If routine dosimeters are to be located on the surface of

product then measurements should be made to evaluate the magnitude of the effects described above.

An alternative approach, which avoids these difficulties, is to irradiate routine dosimeters separate from product in well defined locations within purpose built assemblies which are transported through the irradiator with the product. Such assemblies could be calorimeters, or phantoms suitable for holding routine dosimeters. In the case of a phantom it is important that the geometry of the assembly is reproducible (i.e. that the dosimeters can be easily located in the same place in the phantom each time it is used) and it is advisable that the position of dose measurement is not on the surface of the assembly where dose gradients can affect the reproducibility of the dosimeter reading.

4. Frequency of routine dosimetry & number of dosimeters used

4.1. General

The frequency of routine dosimeter measurements determines how much product is in jeopardy of not being released if a dose measurement is outside the specified limits. The factors that need to be taken into account when deciding the frequency of routine dosimetry are different for gamma and EB irradiation (see sections 4.2 and 4.3 below). However, in both cases the number of dosimeters used for each measurement is a balance between cost and precision. As the number of dosimeters increases the precision of the measurement derived from the average of the dosimeter readings increases. For example the standard deviation of the mean of the readings from N dosimeters can be expected to be approximately $1/\sqrt{N}$ times the standard deviation of a reading from a single dosimeter. Such a reduction in the intrinsic spread of dosimeter readings could have a significant impact on the setting of acceptance criteria for routine dosimeter readings with consequent impact on the cost of irradiation. In addition the use of more than one dosimeter helps to minimise the effect of a spurious dosimeter reading (an outlier) which might otherwise jeopardise the release of product. However, an increasing number of dosimeters for each measurement implies an increasing cost for routine dosimetry. This cost must be balanced against the savings that flow from the increased precision of measurement and the reduced risk of not releasing product as a result of spurious dosimeter readings.

4.2. Gamma irradiators

Clear direction is provided by both the European (EN552) and International (ISO11137) standards as to the frequency of routine dosimetry measurements in gamma irradiators. In particular EN552 states (section 6.1.2) "*There shall be at least one dosimeter in each product path in the irradiator"*.

In addition to this minimum requirement it should be noted that increasing the frequency of routine dosimetry reduces the amount of product associated with each dosimeter reading. However, this must be balanced in each individual case against the increased cost of the dosimetry.

It should be noted that the number of routine dosimeters may also be affected by operational matters such as the product mix in the irradiation cell. This is particularly the case in contract irradiation plants where customers may require at least one routine dosimeter associated with each consignment of product. For example, small consignments of several product types each

requiring a routine dosimeter would result in a larger number of routine dosimeters being used than for one large consignment of product.

4.3. EB irradiators

In electron beam irradiators only a small volume of product, representing a fraction of one irradiation container, is in the electron beam at any one time. It is therefore not possible in any practical way to have the irradiation process monitored by routine dosimetry at all times. However, it is a requirement in EB irradiators that the critical plant parameters (electron energy, average beam current, scan width and conveyor speed) are monitored to ensure that all product is processed according to specification. In the case of EB irradiators routine dosimetry acts essentially as a periodic check of the effectiveness of the critical plant parameter monitoring system. In this case increasing the frequency of routine dosimetry reduces the average time following the development of a fault in processing before the process deviation is observed, minimising the amount of product affected. As in the case of a gamma irradiator, this must be balanced in each individual case against the increased cost of the dosimetry.

In most EB facilities an automatic control system is used to maintain a fixed relationship between the output current from the accelerator and the speed of the conveyor system that transports the product through the beam. The purpose of such a system is to ensure that the electron fluence (the number of electrons delivered per unit area of the surface of the product) stays at the appropriate value for the product being processed. The system may also monitor the width of the scanned beam to ensure that it is wider than the product being irradiated. Wherever practicable there should be at least one routine dosimeter reading between each change in the settings of these parameters (i.e. a change in scan width or electron fluence at the surface of the product). EN552 notes (section 6.2.2) that *"Commonly, dosimeters are placed on at least the first middle and last irradiation container processed using the same irradiator operating conditions"*.

In the case of plants where the number of such changes are frequent and perhaps automatically controlled (e.g. by bar-coding on the product boxes) it may be necessary to use other criteria for determining the frequency of routine dosimetry such as specifying a fixed period of time between routine dosimeter measurements. Alternatively consideration should be given to reducing the number of parameter changes by exploring different product scheduling arrangements.

Additional dosimetry may need to be considered following a process interruption on an EB plant, but this depends on the nature of the irradiator and its characteristics as determined during installation qualification.

5. Relationship between dosimeter readings and delivered dose

In the absence of any measurement uncertainties, routine dosimeter readings could be used in a simple way to determine whether irradiated product should be released. The routine dosimeter readings would be multiplied by the ratio (determined during dose mapping) between the dose at the minimum dose location and at the routine dosimeter location to give the minimum dose in the product. Similarly the readings would be multiplied by the ratio between the dose at the maximum dose location and at the routine dosimeter location to give the maximum dose in the product. If the maximum and minimum doses determined in this way were within the range specified for the product, the product could be released.

Conversely, as stated in EN552 (section 6.1.2) "*Any dosimetric reading indicating a dose outside the specified limits shall be investigated....*"

In practice, however, variations in routine dosimeter readings do not just reflect the variation in dose delivered in the product. The measurement of dose using any dosimetry system has intrinsic uncertainties which would give rise to variations in the dosimeter readings even if the dose delivered to the dosimeters were unchanged. Similarly there can be changes in the dose delivered to product which may not be reflected in the dose recorded by the dosimeter (e.g. variations in product packing in a region well away from a routine dosimeter). In addition there will be an overall uncertainty in the absolute magnitude of the dose recorded by the routine dosimeters due to the fact that their calibration will involve uncertainties.

These facts make the interpretation of routine dosimeter readings and the setting of acceptance criteria more complex than the simple situation described above. In particular it is not possible to produce acceptance criteria for dosimeter readings that ensure that ***all*** product released has received doses within the specified range. However it is possible to specify criteria which ensure ***to a specified confidence level*** that product released has received doses within the specified range. One of the first and crucial decisions to be made in setting acceptance criteria for routine dosimetry is the choice of confidence level against which to release product. Clearly the choice of this confidence level has regulatory implications. It also has practical consequences - a high confidence level can impose severe economic penalties (operating irradiators with a very large "safety margin"). The requirement to allow such a safety margin above the minimum (sterilising) dose to account for uncertainties may also conflict with a similar requirement to allow a safety margin below a maximum dose (to limit deleterious radiation damage of materials). *In extremis* the conditions for maximum and minimum dose may overlap!

5.1. Sources of uncertainty and variability.

In this section the sources of uncertainty and variability that are involved in the interpretation of routine dosimeter readings are grouped into four categories. Although this division is arbitrary it will assist in the discussion and interpretation of dosimetry measurements set out in sections 5.2 and 5.3. It also provides a framework within which the considerations involved in setting acceptance criteria might be analysed. Further guidance on the estimation and handling of uncertainties, together with standard terminology, particularly for dosimetry, can be found in the ASTM standard E1707[5]. It is also worthwhile noting that human error can contribute to all the following categories. This needs to be recognised and minimised by carefully designed procedures, staff training and monitoring.

A. **Dose measurement uncertainty due to calibration.** This is the uncertainty associated with the calibration of the routine dosimetry system that is used. The contributions to this uncertainty depend on the way in which dosimeters are calibrated, on the traceability path to the National Standard and on the primary standards themselves. However, they may well include some of the following examples (not in order of importance):

- Uncertainties in the Standard Radiation Field at Calibration laboratory.
- Intrinsic uncertainty in response of the transfer standard dosimeter.
- Uncertainty associated with delivering the same dose to transfer and routine dosimeters.
- Uncertainties associated with the fit of a calibration curve to the calibration data.
- Environmental effects on dosimeters.

B. **Dose measurement uncertainty due to dosimetry system variability**. If an identical dose was delivered to samples of dosimeters used for routine dosimetry, from the same batch and with the same calibration, then the doses read from the dosimeters would show a spread due to a variety of factors associated with the dosimetry system itself. This uncertainty in the measurement of dose has a number of contributory factors which may include (not in order of importance):
    - Intrinsic variation in dosimeter response.
    - Uncertainties associated with determination of dosimeter thickness.
    - Variations in the equipment used to read the dosimeters.
    - Variations in the environmental conditions of irradiation of dosimeters.
    - Variations in the conditions of or length of post-irradiation storage prior to read-out

C. **Product variability.** If perfect dosimeters were repeatedly used to dose map nominally identical product loads in irradiation containers in a perfect irradiator the resulting dose-maps would not be identical. Contributions to this variation between one dose map and another may include (not in order of importance):
    - Variations in manufactured product.
    - Variations in packing and packaging of product.
    - Reproducibility of dosimeter placement.

D. **Plant variability.** This would give rise to a spread of dosimeter readings if perfect dosimeters were repeatedly located at perfectly defined locations and subjected to irradiation at the same plant parameter settings.

In a gamma irradiator the factors which contribute to such variations include (not in order of importance):
    - Variations due to the different product loading in the cell
    - Variations in timer performance
    - Variations in conveyor movement

Note: The variation in product loading in a gamma irradiator is controlled by the plant operator. Even so it is still the most important contribution to this variability.

In an EB irradiator the factors which contribute to such variations include (not in order of importance):
    - Variations in electron beam energy and current
    - Variations in scan width
    - Intrinsic uncertainties due to imperfections in conveyor speed (servo) control system

5.2. Combinations of sources of uncertainty and variability

The four categories of uncertainty and variability listed above do not always all contribute to the observed spread of dosimetry measurements made on the plant. Indeed the knowledge of which categories contribute in which situations, together with an understanding of how uncertainties combine, may help in the estimate of the magnitude of the contribution of individual categories. (A brief discussion of the combination of uncertainties is given in appendix A to this paper).

5.2.1. Dose mapping:

One of the primary aims of product dose-mapping is to determine the ratio between the dose measured at a routine monitoring position and the dose delivered at the extreme dose locations. Provided that all the dosimeters used in the exercise are from the same batch, with the same calibration, then primarily dosimeter system variability and product variability will contribute to the observed spread in this ratio. Plant variability will also contribute but it effect should be small. The spread in this ratio is best characterised (i.e. the standard uncertainty determined) if replicate dose maps are made. These replicate dose maps need not be as extensive as the first map. They need concentrate on measurement in the regions of minimum and maximum dose identified from the initial full dose map. Alternatively, a thorough quantitative understanding of the characteristics of the various contributions to this spread (determined from previous measurements) may enable an estimate of the standard uncertainty to be made.

Once this spread has been characterised it is possible to make an estimate, to any desired confidence limit, of the extreme values of the ratio between the dose measured at the routine monitoring position and that delivered at the minimum and maximum dose locations.

5.2.2. Routine dosimetry

In a routine dosimetry measurement all four categories described above will contribute to the uncertainty in the routine dosimeter reading as a measure of the absolute dose delivered to the product. However, the categories that contribute to the ***observed*** spread of the routine dosimeter readings will depend on the measurement that is being made.

Measurements of the dose at the routine monitoring position for the same irradiation conditions with dosimeters from the same batch and with the same calibration on different irradiation containers will exhibit a spread characteristic of the combination of dosimeter system, plant and product variabilities.

Note: In a gamma irradiator there is an expected variation in routine dosimetry readings as a function of time due to the decay of ^{60}Co between changes in timer settings. In practice the conveyor timer settings are adjusted to take account of this after a fixed period (for example a ~1% correction once each month). In order to characterise the purely stochastic uncertainties in routine dosimetry measurements, account should be taken of this effect by re-normalisation of the results to a standard time before attempting to characterise the uncertainties of the results.

If more than one dosimeter from the same batch and with the same calibration are placed in the same routine monitoring position then there will be a spread in the observed readings that is affected only by the dosimetry system variability. One way to characterise this is to examine the spread of the individual readings divided by the average reading for each replicate set of dosimeters. The resulting ratios derived from a number of different routine dosimetry measurements can then be combined to characterise this uncertainty. The standard uncertainties obtained in such an exercise should be consistent with those observed during the dosimeter calibration exercise when a number of dosimeters are irradiated at each of a number of different doses.

5.2.3. Dosimeter batch changes

As noted above, the uncertainty in a dosimeter reading due to the calibration of the dosimetry system will not contribute to the observed spread in dosimeter readings in either dose mapping or routine dosimetry. These uncertainties will appear, however, when routine dosimeter batches are changed and the new batch is re-calibrated. They will appear as a shift in the mean routine dosimeter readings observed for particular irradiator operating conditions. A change is

most easily observed if dosimeters from the two batches are run together for a transition period covering the change from one batch to the other.

As batch changes are infrequent (typically once a year or less) it is not practical to use repeated measurements of the change in dosimeter readings from batch to batch to characterise this uncertainty. Instead the magnitude of the standard uncertainty due to calibration should be estimated separately and the magnitude of the observed change in dosimeter readings compared with this value in order to determine whether the observed change is indicative of a problem with the dosimetry system rather than just the random variations expected within the calibration uncertainties.

This highlights the need for dosimetry uncertainties to be built into routine processing monitoring and control so that the changes described above which can appear at dosimeter batch change do not have operational significance.

The expected magnitude of the uncertainties associated with dosimeter calibration can be estimated using the techniques set out in ASTM Standard E1707[5] or as discussed in the Guidelines produced following the recent European dosimetry intercomparison project[6]. Guidance on estimating uncertainties associated with traceability to a National Standard should be provided by the Standards laboratory involved in the calibration of the routine dosimetry system.

5.3. Relating routine dosimeter readings to delivered dose

The above discussions set out the uncertainties and variabilites involved in the interpretation of routine dosimeter readings and the situations in which their presence is manifest. In order to interpret routine dosimetry measurements, it is important to understand the contributions made by the various categories of variability and uncertainty and particularly to characterise quantitatively the combinations that contribute to the uncertainty in routine to extreme dose ratios and the calibration uncertainties.

The most probable value for the minimum dose delivered is the product of the routine dosimeter reading multiplied by the ratio (determined during dose mapping) derived from the dose at the minimum dose location and at the routine monitoring position. Similarly the most probable value for the maximum dose delivered is the product of the routine dosimeter reading multiplied by the ratio (determined during dose mapping) derived from the dose at the maximum dose location and at the routine monitoring position.

However, in order to determine the minimum or maximum delivered dose at a specified confidence limit, this most probable value must have the standard uncertainty for the measurement multiplied by the appropriate coverage factor (see Appendix A) subtracted from it (in the case of the minimum dose) or added to it (in the case of the maximum dose).

The appropriate standard deviation will be the result of the combination of the standard uncertainty in the minimum (or maximum) to routine dose ratio, the standard uncertainty of the dose recorded by the routine dosimeter (the calibration uncertainty) and the standard uncertainty of the dosimeter variability. As pointed out in section 4 of this document, the last of these contributions can be minimised by the use of replicate dosimeters. The three standard uncertainties would be combined as set out in Appendix A. An illustration of this is set out in the example overleaf.

DOSE MAPPING RESULTS

In a dose mapping exercise 5 nominally identical dose maps were carried out. The ratios between the doses at the extreme dose locations and the routine monitoring position were as listed in the table below.

	Minimum/routine dose ratio	Maximum/routine dose ratio
Dose map 1	0.835	1.125
Dose map 2	0.880	1.115
Dose map 3	0.825	1.105
Dose map 4	0.880	1.150
Dose map 5	0.830	1.055

The mean and standard uncertainties (standard deviations) of the extreme to routine dose ratios determined from this were:

Minimum dose/routine dose: Mean: 0.850 Standard uncertainty: 0.012 (1.5%)
Maximum dose/routine dose: Mean: 1.110 Standard uncertainty: 0.016 (1.4%)

ROUTINE DOSIMETRY RESULTS

For one particular batch of the same product irradiated in the same configuration as for the dose mapping exercise the routine dosimeter reading (average of 3 dosimeters) was: 32.1kGy

At this dose the standard uncertainty due to calibration is calculated to be: 1.5%.

The standard uncertainty for a single dosimeter reading at this dose is estimated, from the performance of the dosimeters during the calibration exercise, to be: 2.0%.
The standard uncertainty of the average of the 3 dosimeters used for routine dosimetry is therefore estimated to be: $2.0 / \sqrt{3} = 1.15\%$

The most probable doses delivered to the product are:

Minimum dose: 0.850 x 32.1 = 27.3 kGy
Maximum dose 1.110 x 32.1 = 35.6 kGy

To obtain the overall standard uncertainties for each of these doses the standard uncertainties due to the dose mapping, calibration and dosimetry variability (expressed as a fraction of the value) must be combined in quadrature :

Standard uncertainty for minimum dose: $\sqrt{(0.015^2 + 0.015^2 + 0.0115^2)} = 0.024$ (2.4%)
Standard uncertainty for maximum dose: $\sqrt{(0.014^2 + 0.015^2 + 0.0115^2)} = 0.024$ (2.4%)

Taking into account these uncertainties and using for example a coverage factor of 2 (confidence level ~95%) the minimum and maximum doses to the product are:

Minimum dose: 27.3 - (2 x 0.024 x 27.3) = 26.0 kGy
Maximum dose: 35.6 + (2 x 0.024 x 35.6) = 37.3 kGy

Hence at the 95% confidence level the minimum dose is >26.0kGy and the maximum dose is <37.3kGy, but the most probable dose range is 27.3 - 35.6 kGy.

NOTES

In the above example, the **standard deviation of the mean ratio** ($\sigma_o/\sqrt{N}$) of the five dose maps has been taken as the dose mapping uncertainty. This approach is valid if the observed scatter arises largely from the ability to measure the ratio, rather than variability in the ratio itself. If the observed scatter in the five dose maps arises from a genuine variability in the ratio due to product differences, then the **standard deviation of the observed ratios** (σ_o) should be taken as the dose mapping uncertainty.

The above example assumes approximate equivalence between a coverage factor of k=2 and a confidence interval of 95%. This equivalence will break down if the combined uncertainty is dominated by one component, which itself is based on only a few observations (i.e. only has a small number of degrees of freedom). This may happen in radiation processing applications if, for example, the dose mapping uncertainty dominates, and is based on only a small number of independent dose maps. In such situations, it may be possible to improve the estimate of dose mapping uncertainty by pooling uncertainty data from dose maps carried out on different products from the same product family.

Before variations in measured dose are used to set criteria for product release or for process control, consideration needs to be given to the degree of correlation between these changes in

routine dosimeter reading and the dose delivered to the product. To illustrate this consider the following two extreme situations. In practice, the situation in a real plant will fall somewhere between these two extremes.

First the case in which the observed spread in routine dosimetry measurement is dominated by uncertainties in dose delivered due to plant variability. In these circumstances the variation in routine dosimeter readings correlate strongly with the variation in dose delivered by the plant. An example of this situation might be a gamma plant in which changes in routine dosimeter reading are dominated by variations in the product mix in the irradiator. If, in addition to the above, the variations in delivered dose due to plant variability are large compared to the uncertainties associated with product variability, then routine dosimeter readings will correlate strongly with the maximum and minimum dose delivered to the product i.e. individual routine dosimeter readings are a good monitor of the dose delivered to the product. An increase in routine dosimeter readings from irradiation of one batch of product compared to those from irradiation of another batch of the same product would correspond to an increase in the maximum and minimum dose delivered to the product

Contrast this with the case where the uncertainty due to plant variability is similar in magnitude or smaller than the uncertainty due to dosimeter variability and product variability. In this situation, when the irradiator is operating correctly (i.e. the process is "in control"), there will in general only be a weak correlation between the variation in routine dosimeter readings and the variation in minimum and maximum doses received by product. This is a result of the various categories of uncertainty described in section 5.1 being essentially un-correlated. A routine dosimeter reading *above* the mean reading expected for the plant operating conditions could result from a delivered dose from the plant *below* the expected mean but read as high due to random variations in the routine dosimetry system. In addition, totally un-correlated variations in the packaging or manufacture of the of the product could lead to the minimum dose delivered to the product itself being below or above the expected mean for the irradiator operating conditions. Under these circumstances, unless there is a serious fault in the operation of the irradiator, routine dosimetry acts as a monitor of whether the irradiation process is "in control" rather than as a direct monitor of the dose received by the product.

As stated above, the situation in most real irradiation plants will fall between these two extremes. However, the approach taken in the interpretation of routine dosimeter results will depend on the extent to which the situation most nearly conforms to either of these extremes.

6. CONCLUSIONS

This document has attempted to identify the main sources of uncertainty in measurement and variability in delivered dose that are involved in the interpretation of routine dosimeter readings. It has also set out the way in which such factors manifest themselves.

In order to proceed further towards practical guidelines for routine dosimetry that recognise and take into account these factors, a number of issues need to be addressed.

- What are the magnitudes, in actual irradiation plants, of the various sources of uncertainty and variability identified?
- What are the consequences of the relative magnitude of the different factors for the correlation between routine dosimeter readings and dose delivered in product in these plants?

- In the light of the above what are appropriate statistical tools and techniques for interpreting routine dosimetry?
- What is an appropriate confidence level to work to when taking into account uncertainties in routine dosimetry?

In answering all of the above questions an overriding consideration must be the impact of any change in procedures on the operation of existing plants. This should include the regulatory, operational and financial impact.

Appendix A. Combination of uncertainties.

In order to establish the accuracy of any measurement, it is necessary first to identify and then quantify all possible components of uncertainty. This is most easily done by considering in turn each contribution to the uncertainty and assessing its magnitude. The uncertainty associated with the overall measurement can then be calculated by combining the individual components. The philosophy used is to ascribe to each component of uncertainty an effective standard deviation, known as a standard uncertainty, and it is these standard uncertainties that are then combined to produce the overall uncertainty.

When dealing with statistical effects, such as the random scatter between replicate dosimeters, the concept is clear and it is straightforward to calculate the relevant standard uncertainty. Such components of uncertainty are known as Type A components.

Other components of uncertainty, for example the effect of irradiation temperature on dosimeter response, are not easily calculated from a set of statistical data and a more subjective approach has to be taken. A common situation is that prior knowledge indicates that an effect is very unlikely to be greater than ±a%, but no other information is available as to its exact value. An alternative way of stating this is to say that there is a 100% probability of the effect being between ±a%, and a 0% probability of it taking any other value. If, in addition, the value is equally likely to be anywhere between ±a% then this is known as a rectangular probability distribution and an effective standard deviation can be calculated for it. In such a situation the value of the standard deviation can be taken as a/√3. Components of uncertainty derived by non-statistical methods, such as this, are known as Type B components.

The combined uncertainty associated with a particular measurement (u_c) is obtained by summing in quadrature the individual component standard uncertainties (u_1, u_2, etc.) i.e. by taking the square root of the sum of the squares of the individual components:

$$u_c = \sqrt{(u_1^2 + u_2^2 + u_3^2 + \ldots\ldots)}$$

It should be noted that this expression is strictly only valid for uncertainties that are un-correlated.

In reporting the uncertainty associated with a particular measurement, the level of confidence that the correct result will lie within the reported range needs to be given. Historically, uncertainties have been reported based on either a 95% or a 99% probability that the correct value is within the range. The accurate calculation of such values is, however, extremely complex and current practice[5] is to report standard uncertainties multiplied by a *coverage factor (k)* of either 2 or 3. For most situations, a coverage factor of 2 is very close to a 95% confidence interval and a coverage factor of 3 is very close to a 99% confidence interval.

References

[1] **European Standard EN552.** "Sterilization of Medical Devices - Validation and routine control of sterilization by irradiation". European Committee for Standardization, rue de Stassart 36, B-1050 Brussels, (1994).

[2] **ISO Standard 11137,** "Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization", International Organisation for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland, (1995)

[3]**ASTM Standard E1261,** " Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing", American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428, USA (1994).

[4]**Guidance Notes on the Dosimetric Aspects of Dose-Setting Methods.** The Panel on Gamma and Electron Irradiation, 595 Chesham House, 29-30 Warwick Street, London, W1R 5RD, United Kingdom (1997).

[5]**ASTM Standard E1707,** "Standard Guide for Estimating Uncertainties in Dosimetry for Radiation Processing.", American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428, USA (1995).

[6]**NPL Report CIRM 29**, "Guidelines for the Calibration of Dosimeters for use in Radiation Processing.", P Sharpe and A Miller, National Physical Laboratory, Queens Road, Teddington TW11 0LW, United Kingdom (1999)