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Lithium formate EPR dosimetry

Properties and applications in radiotherapy

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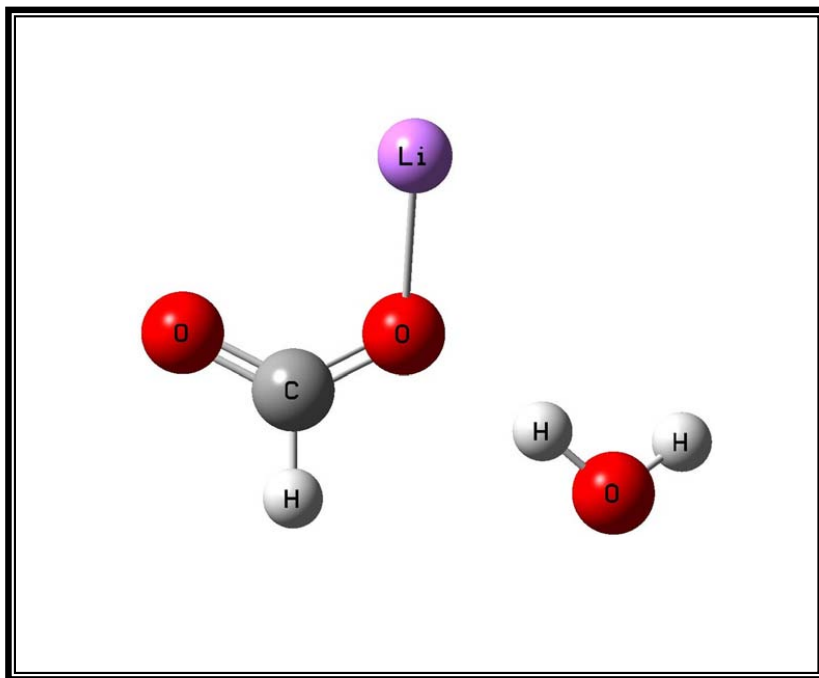
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LIST OF PAPERS

- I Malinen E, Waldeland E, Hole E O and Sagstuen E
LET effects following neutron irradiation of lithium formate EPR dosimeters
Spectrochimica Acta Part A **63** (2006) 861-869
- II Waldeland E, Hole E O, Stenerlöw B, Grusell E, Sagstuen E and Malinen E
Radical formation in lithium formate EPR dosimeters following irradiation with protons and nitrogen ions
Radiation Research **174** (2010) 251-257
- III Waldeland E, Helt-Hansen J and Malinen E
Characterization of lithium formate EPR dosimeters for high dose applications – comparison with alanine
Radiation Measurements **46** (2011) 213-218
- IV Malinen E, Waldeland E, Hole E O and Sagstuen E
The energy dependence of lithium formate EPR dosimeters for clinical electron beams
Physics in Medicine and Biology **52** (2007) 4361-4369
- V Waldeland E, Hole E O, Sagstuen E and Malinen E
The energy dependence of lithium formate and alanine EPR dosimeters for medium energy x rays
Medical Physics **37** (2010) 3569-3575
- VI Waldeland E, Hörling M, Hole E O, Sagstuen E and Malinen E
Dosimetry of stereotactic radiosurgery using lithium formate EPR dosimeters
Physics in Medicine and Biology **55** (2010) 2307-2316

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Lithium formate monohydrate

1 INTRODUCTION

Cancer is a serious disease which in many cases is lethal. Treatment of cancer may involve chemotherapy, surgery, radiotherapy or combinations of these modalities. The use of radiotherapy has been increasing in Norway the last 20 years, from covering only half of the needs around 1990 to almost 80% in 2007 (Jetne *et al* 2009, Lote *et al* 1991). It is expected that around 30% of all patients diagnosed with cancer should need initial radiotherapy (ACRO 2009), while over half of the patient population with cancer should receive radiation during the period of illness (Delaney *et al* 2005, WHO 1980).

Radiation as treatment of cancer was taken into use immediately after ionizing radiation from x-ray tubes and radioactive isotopes were discovered over a century ago. From the relatively simple use of x-ray tubes and radioactive materials to treat cancer, radiation therapy is now a highly sophisticated modality for treatment. Traditionally, radiotherapy has been performed using radioactive isotopes (e.g., ^{60}Co , ^{226}Ra , ^{192}Ir and ^{137}Cs), x-ray tubes or high energy electron or photon generators. The radiation may be delivered externally or internally. The latter, called *brachytherapy*, is performed by introducing radioactive sources into, or close to, the tumour, while external beam therapy today usually is provided by x-ray tubes or high energy x-ray and electron generators called *linear accelerators*. Superficial tumours may be treated with low energy x rays, tumours at shallow or medium depths in the patient can benefit from linear accelerator electron treatment, while deep seated tumours and tumours with a difficult or non-localized position are normally treated with high energy photons, also from a linear accelerator.

The technological developments in radiotherapy are mainly focused around better field shaping, high precision delivery techniques and devices, and better imaging modalities, but also new accelerator principles are being introduced. In addition to electron and photon beam radiotherapy, neutrons (Barth *et al* 2005), protons and heavier ions or hadrons (Durante & Loeffler 2010) have been used. Using hadrons, less normal tissue receives high radiation doses compared to conventional photon therapy, due to the localized energy deposition by these particles as compared to photons.

Ionizing radiation is radiation capable of ionizing atoms or molecules, i.e., releasing electrons from their bound states. When a medium is exposed to ionizing

radiation, energy is transferred through ionizations. In radiotherapy, the energy transfer from the radiation field to tissue molecules is the principal interaction of interest. Such interactions may cause cell damage or cell killing. The purpose of radiotherapy is to transfer enough energy to the tumour and, at the same time, as little as possible to the surrounding normal and healthy tissue. The absorbed dose resulting from irradiation is measured in terms of the energy imparted per mass of tissue, with unit Gray (1 Gy = 1 J/kg). Different kinds of radiation show distinctly different interactions with tissue. These differences result in characteristic energy deposition patterns for different types of radiation in biological matter, e.g., water (figure 1).

The art of estimating radiation doses is called dosimetry. Different approaches for measuring the dose may be applied. A direct measure of dose is provided by calorimetry, where the temperature change in a medium, e.g., water or graphite, is measured while exposed to radiation. This method is difficult for practical measurements in radiotherapy, and other procedures are needed.

Recommendations of the minimum and maximum doses which should be delivered to a tumour, is normally within only a few per cent from the prescribed tumour dose (IAEA 2001, ICRU 1993, ICRU 1999, ICRU 2004, ICRU 2010, Wambersie 2001), and hence accurate dosimetry is crucial. The reference method for measurements of absorbed radiation dose in radiotherapy is ionometry, that is, measurements with ionization chambers. Such chambers collect ionizations in air or another medium and measure the electric current when the radiation induced ions are released under a high voltage. High precision dosimetry performed worldwide requires standardized methods and equipment, and dosimetry protocols are available (Almond *et al* 1999, IAEA 2001). In addition, national and international standardized dosimetric calibration laboratories are established, among other purposes; to ensure a common dosimetry practice in hospitals using ionizing radiation.

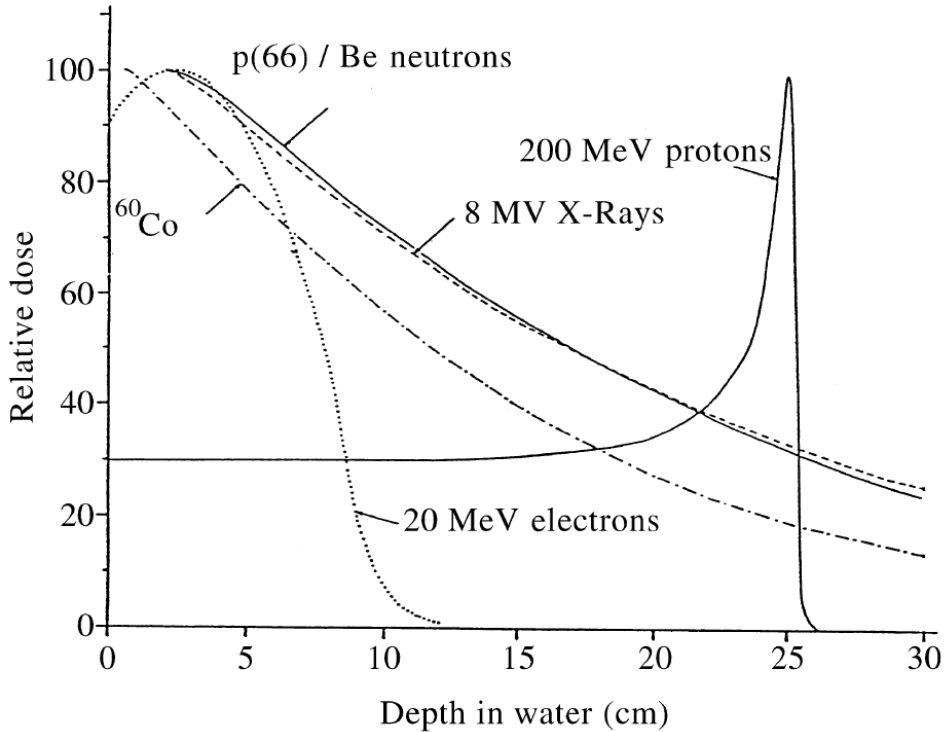


Figure 1: Percent depth dose curves for different types of radiation used in radiation therapy as a function of penetrating depth in water (Orecchia *et al* 1998). Typical beam qualities of photons (^{60}Co and 8 MV from a linear accelerator), electrons (20 MeV from a linear accelerator), neutrons and protons are displayed. The 200 MeV proton beam displays the characteristic 'Bragg-peak' at the end of the beam track, which is similar for all monoenergetic ion beams interacting with matter.

There are several dosimetry systems available, and normally each system has its advantages and disadvantages compared to other systems. Important characteristics are sensitivity, reproducibility, adequate size and minor or well known dependence on radiation beam quality. Some ionization chambers fulfil all these requirements, which make them recommendable. But ionization chambers have some limitations, like the need for cables and inappropriate sizes to be used for measuring inside a patient – *in vivo* – or a phantom, or for high resolution 2D or 3D measurements of dose distributions. High resolution measurements could e.g., be performed with films or gels, while point measurements within a phantom could be provided by thermoluminescence (TL)

dosimeters or electron paramagnetic resonance (EPR) dosimeters. Films, gels, TL and EPR dosimeters are all *offline* dosimetry systems because a readout has to be performed *after* the irradiation takes place, while electrometers collect the responses of ionization chambers (or semiconductor diodes) *online*.

The positive and negative ions produced in matter following ionizations are in most cases highly unstable species. A chain of chemical reactions usually follow the primary charge separation, often involving the formation of free radicals (or simply radicals), which are molecules with one or more unpaired electrons. In some crystalline lattices, large amounts of stable (or quasi-stable) radicals may be induced following irradiation. In EPR (Electron Paramagnetic Resonance) dosimetry, the irradiated dosimeter, containing radiation induced radicals, is placed in a strong magnetic field while exposed to microwaves. Scanning the microwave frequency (at a fixed magnetic field strength) or the magnetic field (at a fixed microwave frequency) results in a resonance spectrum. The spectrum intensity may be related to the amount of radiation induced radicals in the dosimeter, which again is a function of the absorbed dose. Examples of EPR dosimeters range from solid state dosimeters to biological or organic dosimeters like tooth enamel and food (Fattibene & Callens 2010, Kleinerman *et al* 2006, Mladenova *et al* 2010). The process of EPR dosimetry is schematically illustrated in figure 2.

The amino acid L- α -alanine (alanine) was first proposed as an EPR dosimeter in 1962 (Bradshaw *et al* 1962), and the practical use of alanine EPR dosimetry has been reported for some decades (Regulla 2000, Regulla & Deffner 1982). When irradiated, large amounts of stable radicals are formed in this crystalline dosimeter material (Heydari *et al* 2002, Malinen *et al* 2003a, Malinen *et al* 2003b, Miyagawa & Gordy 1960, Sagstuen *et al* 1997), which is clearly an advantage for EPR spectroscopy. In alanine EPR dosimetry, many different dosimeter shapes have been used. Commercial dosimeters are typically cylindrical (diameter \sim 5 mm), made of a mixture of alanine and paraffin (with the latter acting as binder). Minidosimeters with diameter and height \sim 1 mm (Abrego *et al* 2007, Mack *et al* 2002) and thin alanine films (Furre *et al* 1999, Helt-Hansen *et al* 2005, Olsson *et al* 2002, Xie *et al* 2002, Xie *et al* 1993, Østerås *et al* 2006) have also been employed.

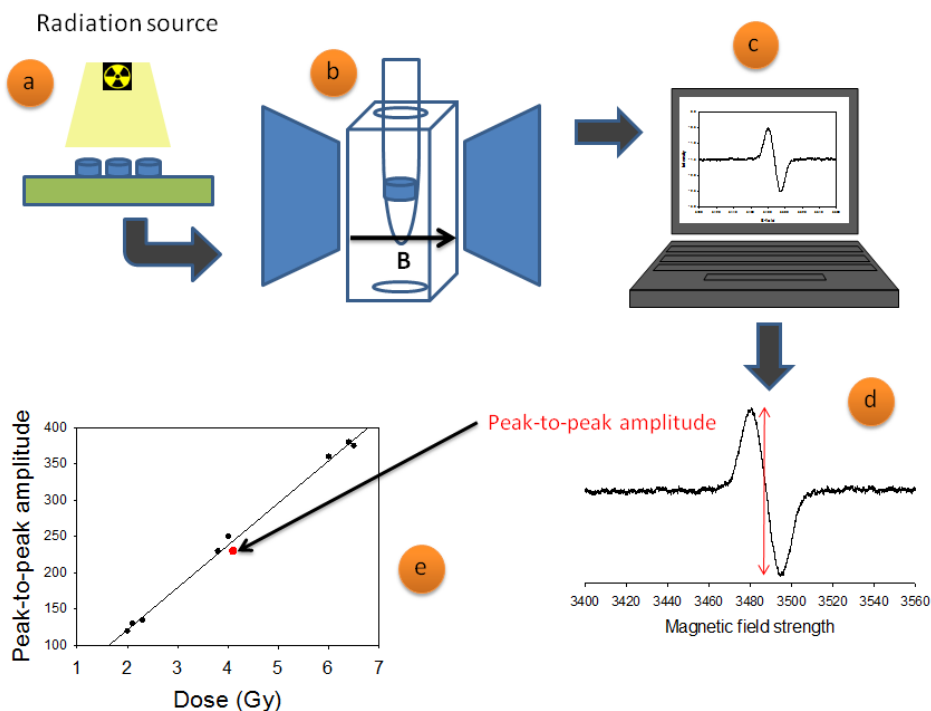


Figure 2: The process of EPR dosimetry. (a) Dosimeters are irradiated with a radiation source and radicals are produced. (b) A dosimeter is placed in a strong magnetic field in an EPR spectrometer. (c) Scanning the magnetic field, a spectrum is recorded. (d) From the EPR spectrum, the peak-to-peak amplitude is found, being a function of the absorbed dose. (e) Combining readings from all dosimeters given known doses (symbols), a calibration regression may be performed (straight line). Using the calibration relation, the dose to dosimeters given unknown doses may be estimated.

The EPR signal from the radicals in irradiated alanine detectors is very stable, with a reported signal fading of commercial dosimeters of less than 1% per year (FWT 2010). EPR readout is a non-destructive type of measurement, and because of their high stability the dosimeters may be stored for long periods (months or years). Alanine dosimeters have very low dependence on irradiation temperature (Desrosiers *et al* 2009, Nagy *et al* 2000, Sharpe *et al* 2009), and the radical formation is nearly independent of dose rate at doses below 10 kGy (Desrosiers *et al* 2008). Furthermore, the EPR signal shows only a very weak dependence on factors like temperature, environmental humidity and time span between irradiation and measurement (Nagy *et al* 2000, Slepetchonok *et al* 2000, Wieser *et al* 1989).

The use of alanine has previously been recommended for high dose measurements (typically over 100 Gy) by the International Atomic Energy Agency, IAEA (Mehta & Girzikowsky 1996) because of its high radical stability and good properties for dosimetry in this dose region. Also, the alanine dosimetry system has been applied for mail-in and e-calibrated dosimetry (ASTM 1999, Desrosiers *et al* 2002). Additionally, it has been suggested as a high precision secondary standard (reproducibility below 0.5% in the 5 – 50 Gy range) for absorbed dose to water (Anton 2005).

Alanine has been used for dosimetry of radiotherapy beams like high energy electrons and photons (Chu *et al* 1989, Ciesielski *et al* 2003, Helt-Hansen *et al* 2009, Kudynski *et al* 1993, Mehta & Girzikowsky 2000, Onori *et al* 2006), and the dosimeter signal has also been studied after irradiation with other beam qualities (Hansen & Olsen 1986, Hansen *et al* 1987, Olko 2002, Waligorski *et al* 1989). Regarding radiation absorption characteristics, alanine has properties quite similar to tissue or water, and thus shows a low energy dependence for high energy electron and photon beams (Anton *et al* 2008, Bergstrand *et al* 2005, Bergstrand *et al* 2003, Zeng *et al* 2004, Zeng *et al* 2005). However, for kilovoltage x-ray beams, significant energy dependence has been found (Alexandre *et al* 1992, Chen *et al* 2008, Coninckx *et al* 1989, Hansen *et al* 1989, Regulla & Deffner 1982).

Applications of alanine dosimetry in radiotherapy require a thorough uncertainty analysis at relevant dose levels, which has been addressed in several studies (Anton 2006, Bartolotta *et al* 1993, Bergstrand *et al* 1998, Nagy *et al* 2002). Typical uncertainties reported are 1.5 – 4% for doses between 1 – 5 Gy (Nagy *et al* 2002). Furthermore, methods for performing high precision alanine dosimetry in radiotherapy have been reported (Hayes *et al* 2000). The methods which gives the highest precision seem somewhat time consuming and impractical for daily use. Alanine dosimetry has been used for numerous applications in radiotherapy, e.g., brachytherapy (Anton *et al* 2009, Olsson *et al* 2002), advanced radiotherapy techniques (Bailat *et al* 2009, Mack *et al* 2002, Rosser & Bedford 2009) and small field dosimetry (Abrego *et al* 2007). Alanine EPR dosimetry has been assessed as feasible for clinical dosimetry (Ciesielski *et al* 2003, Schultka *et al* 2006, Wagner *et al* 2008).

Despite of its favourable properties, irradiated alanine has a relatively complex EPR spectrum of multiple resonances. As the common dosimetry procedure is to extract

the peak-to-peak amplitude of the central resonance line, this leads to reduced sensitivity of the alanine dosimeter compared to a dosimeter yielding a single-line resonance. For typical radiotherapy doses (< 5 Gy), accurate alanine dosimetry becomes time consuming when the goal is a high signal to noise ratio. Hence, more sensitive dosimeter materials are needed for EPR dosimetry in the radiotherapy and radiation protection dose ranges.

Different dosimeter materials have been tested for EPR dosimetry (Lund *et al* 2002, Vestad *et al* 2003). Among these materials, the formic acid lithium formate monohydrate (lithium formate) is a compound with several favourable properties compared to alanine. For instance, lithium formate is 5-6 times more sensitive (Vestad *et al* 2003) and has an atomic composition closer to water (Vestad *et al* 2004b), which is the medium of interest in clinical dosimetry. This thesis presents work performed to investigate some of the properties of lithium formate that is needed to establish lithium formate EPR dosimetry as a suitable method for clinically relevant measurements.

2 BACKGROUND

2.1 Dosimetry

The dose D at a point of interest in matter with infinitesimal mass dm is given by

$$D = \frac{d\varepsilon}{dm}, \quad (1)$$

where $d\varepsilon$ is the energy imparted by ionizing radiation. The dose is given in Gray; [Gy]=J/kg. The absorbed dose depends on the material where the dose is deposited. For radiotherapy the human body is the medium of interest, and hence liquid water is chosen as the reference medium for dose measurements and comparisons in basic dosimetry (IAEA 2001). Normally, dose measurements are not performed using the medium of interest as dosimeter material, but by inserting a dosimeter with a different atomic composition into the medium. *Cavity theory* relates the absorbed dose in a dosimeter's sensitive medium (cavity) to the absorbed dose in the surrounding medium in the absence of the cavity. In that way the dose calculated or measured in a specific material different from water may be related to the absorbed dose in water without any additional measurements. Regarding Eq. 1, for practical reasons and under certain assumptions the point of interest may be expanded to a finite volume. The resulting ε is thus the sum of all the particles passing through the volume times the probability that these particles will impart energy times the expected amount of energy imparted per interaction process. For photons, this may be formulated as

$$D = \int_E \Psi'(E) \left(\frac{\mu_{en}}{\rho} \right)_{E,Z} dE, \quad (2)$$

where $\Psi'(E)$ is the photon energy fluence spectrum, E the photon energy and Z the effective atomic number (Attix 1986). $\left(\frac{\mu_{en}}{\rho} \right)_{E,Z}$ is the mass energy absorption coefficient, which is the probability per unit density for interactions resulting in imparted energy near the interaction site. The ratio of $\left(\frac{\mu_{en}}{\rho} \right)$ for three so-called water equivalent dosimeter materials to $\left(\frac{\mu_{en}}{\rho} \right)$ for water is displayed in figure 3 for clinical x-ray beams, normalized to

the ratio for ^{60}Co γ -rays. The figure shows that, especially for low photon energies, differences in absorbed dose between water and different detectors may be expected, even when the detectors are exposed to the same radiation field.

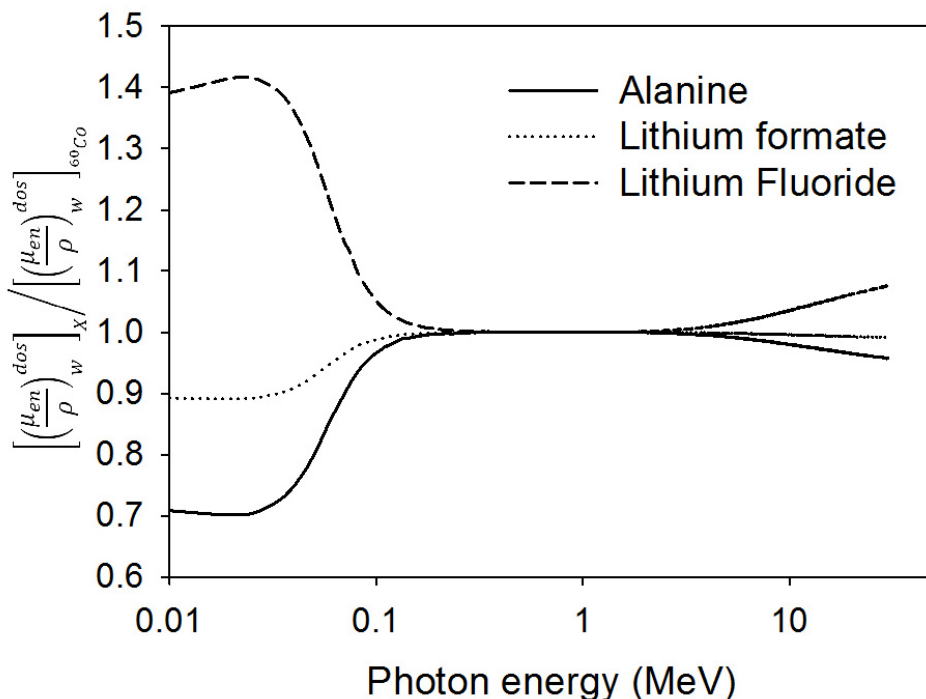


Figure 3: Mass energy absorption coefficients for the three water equivalent dosimeter materials. Coefficients for alanine (solid), lithium formate (dotted) and lithium fluoride (broken line), relative to that for water, are shown. Monoenergetic x rays are assumed. Note that the abscissa is plotted using a logarithmic scale. The values are normalized to the ratio obtained for ^{60}Co γ -irradiation (1.25 MeV).

Analytical calculations of radiation dose such as performed in eq. 2 may be useful, but have limitations when beam geometries and radiation fields are complex. The most recognized computerized method of calculating, or simulating, dose depositions is *Monte Carlo simulations* (Bousis *et al* 2008, Chetty *et al* 2007, Rogers 2006, Zaidi & Ay 2007). The Monte Carlo method for radiation transport calculations utilizes interaction probabilities together with a random number generator, so that each interaction of every particle is

simulated with the accompanying change in primary particle energy and generation of secondary particles. Also, specified radiation sources or treatment machines may be included in the input to the computer program, and statistical calculations of all the particles created, accelerated, scattered and deposited in a volume of interest may be calculated. Limitations of Monte Carlo simulations normally relate to the exactness of the physical modelling (e.g., interaction probabilities) and the variance reduction methods used to speed up the calculations. The processor speed of the computers applied also limits the use. Today Monte Carlo methods are able to perform huge calculations of very advanced systems, and they are to some extent implemented in radiotherapy for dose planning. The use of Monte Carlo calculations for accurate and independent calculations in dosimetry is expected to increase with continuously increasing processor speed of computers.

In this thesis, absolute water-based dosimetry using ionization chambers have mainly been performed according to the International Atomic Energy Agency (IAEA) protocol TRS-398 (IAEA 2001). Measurements of absorbed dose in water, w , in a reference beam quality Q_0 (most often ^{60}Co γ -rays) at reference environmental conditions (temperature, pressure and humidity) and in a specified reference set-up, is governed by the equation (IAEA 2001):

$$D_{w,Q_0} = M_{Q_0} N_{D,w,Q_0} \quad (3)$$

M_{Q_0} is the electrometer readout (given typically in units of nC) and N_{D,w,Q_0} (given typically in units of Gy/nC) is the calibration coefficient of the ionization chamber. When the chamber is positioned in water, the calibration coefficient is the relation between measured charge from ionizations in the air cavity in the chamber and the dose to water in the same point without the chamber present. All experiments not performed in the reference beam quality Q_0 require information about the response of the ionization chamber for the applied radiation quality, Q . For high energy photons or electrons, the dose relation is described by introducing a quality factor k_{Q,Q_0} :

$$D_{w,Q} = M_Q N_{D,w,Q_0} k_{Q,Q_0} \quad (4)$$

M_Q is the corrected electrometer measurement for pressure and temperature conditions deviating from reference conditions. Absolute dose measurements in beam qualities which differ more in interaction nature and energy from the reference beam quality than high energy electrons and photons (e.g., low energy photons, neutrons, protons and other hadrons), need more corrections and the dose estimates have higher uncertainties (IAEA 1987, IAEA 1996, IAEA 2001).

2.2 Beam quality characterization and LET

There are various ways to characterize radiation beam qualities, but international protocols give some recommendations. In this thesis IAEA TRS-398 (IAEA 2001) has been followed for characterization of photons and electrons, while *Linear Energy Transfer* (LET) (ICRU 1970) was used for protons and nitrogen ions.

Following TRS-398 (IAEA 2001), photons and electrons are described by the depth dose characteristics of the respective beams. For high energy photons, the beam quality should be described by the ratio of the dose measured in water at 20 cm depth to that at 10 cm, $TPR_{20,10}$, with constant distance between the source and the ionization chamber. For electrons, the half-value depth in water, R_{50} , is applied. This is the depth in water at which the absorbed dose is 50% of its value at the absorbed-dose maximum. Low energy photons, or kV-photons, should be described by more than one parameter, normally the kilovoltage generating potential (kV), the filtration used and the half value layer (HVL) in Aluminium (Al) or Copper (Cu).

LET, also called restricted stopping power, is a measure of the energy deposited per unit track length in a specific volume when a particle is passing through matter (Attix 1986, ICRU 1970). A limit Δ could be specified for which energy depositions are large enough to escape the volume, and which are not. If $\Delta = \infty$, it means that the volume is large enough to include all energy depositions from secondary electrons released by interaction processes due to the primary particle. When using the term "LET" without specifying the limit, normally the unrestricted LET, or LET_{∞} , is meant. High energy photons and electrons are low-LET beams, while high-LET beams are exemplified by protons, alpha particles and other heavy ions (or hadrons). Typical particle tracks

following low-LET and high-LET beams in a cell nucleus are illustrated in figure 4. As shown, high-LET particles have more or less a straight trajectory and are densely ionizing, while low-LET particles are more scattered and less densely ionizing. Examples of LET-values for different radiation beams are listed in table 1.

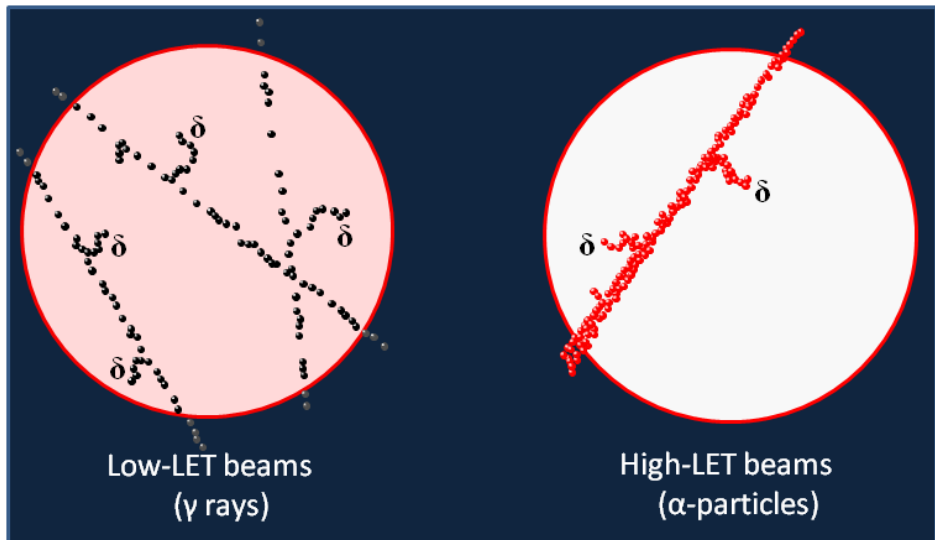


Figure 4: Illustration of typical low-LET and high-LET particle tracks in a cell nucleus (Nittman & Gargioni 2010). The small dots correspond to ionizations.

Accelerated heavy ions do not have a unique LET-value because the LET is dependent on the kinetic energy and the charge of the particle. For instance, the LET-value will be increasing at the end of the particle track, when the energy is rapidly decreasing. However, different ions with the same LET-value do not result in e.g. the same effect on a cellular level (Belli *et al* 1992, Goodhead *et al* 1992), which makes LET-values suboptimal for beam quality specification. A solution for specifying an ion beam quality could be to specify average LET-values over the volume of interest, while additionally specifying particle type and incident energy.

Table 1: Example of LET-values for different beam qualities (ICRU 1970).

Beam quality	LET-value [†] (keV/μm)
⁶⁰ Co γ rays	0.23
2 MeV electrons	0.20
22 MV x rays	0.19
200 kV x rays	1.7
50 kV x rays	6.3
5.3 MeV α-particles (whole track)	43

[†]This is the track-average values of LET in water, with cut-off energy 0.1 keV. For more information, see ICRU report 16 (ICRU 1970).

Following high-LET irradiation, the dose in the track core will be in the region 10^5 - 10^7 Gy. In solid state detectors, such extremely high doses cause a *saturation*, i.e., the energy deposition is so dense that it is impossible to detect all the energy absorbed in the form of radiation induced radicals (Waligorski et al 1989). Saturation may also occur when irradiating a detector with a low-LET beam to extremely high doses, although the microscopic processes causing this effect could be somewhat different (Hansen & Olsen 1985, Nelson 2005, Snipes & Horan 1967, Waligorski et al 1989). So called dose saturation for low-LET beams results in dose response curves typically described by an exponential rise to maximum.

2.3 Energy dependence and relative effectiveness

The energy dependence, F_{Q,Q_0} , of a dosimeter is the dosimeter reading per dose (in terms of dose to water) (r/D_w) in a user beam quality, Q , relative to that for a reference beam quality Q_0 . The energy dependence may be written as follows:

$$F_{Q,Q_0} = \frac{(r/D_w)_Q}{(r/D_w)_{Q_0}} \quad (5)$$

Introducing the dose to the dosimeter, D_{dos} , equation 5 may be written as

$$F_{Q,Q_0} = \frac{(r/D_w)_Q}{(r/D_w)_{Q_0}} = \frac{(r/D_{dos})_Q}{(r/D_{dos})_{Q_0}} \frac{(D_{dos}/D_w)_Q}{(D_{dos}/D_w)_{Q_0}} = G_{Q,Q_0} H_{Q,Q_0} \quad (6)$$

$G_{Q,Q_0} = \frac{(r/D_{dos})_Q}{(r/D_{dos})_{Q_0}}$ is the *relative effectiveness* (or relative radiation yield) of the dosimeter, which relates the dosimeter reading per dose to the dosimeter for a specific beam quality Q to that for a reference beam quality Q_0 . $H_{Q,Q_0} = \frac{(D_{dos}/D_w)_Q}{(D_{dos}/D_w)_{Q_0}}$ is the ratio of absorbed doses in the dosimeter and in water following irradiation with beam quality Q , relative to the same ratio for a reference beam quality. This quantity may be obtained by cavity theory or Monte Carlo simulations. Furthermore, F_{Q,Q_0} is the reciprocal of k_{Q,Q_0} given for ionization chambers, as outlined above (cf. equation 4). For a constant yield of radicals per absorbed dose to the dosimeter for all beam qualities, G_{Q,Q_0} equals unity and F_{Q,Q_0} thus equals H_{Q,Q_0} .

2.4 EPR spectroscopy

Electron paramagnetic resonance (EPR) spectroscopy is a versatile method which may be used for many purposes, among them dosimetry. The method may be used to detect free radicals by microwave induction of electron spin transitions using a phase sensitive detection principle. Here, only the principles of continuous wave EPR spectroscopy are discussed. A more thorough description of the principle of EPR may be found in suitable textbooks (e.g., Atherton 1993).

2.4.1 Resonance

In an idealized sample containing radicals placed in an external magnetic field (with field strength B_0), the unpaired electrons may take two different states due to their magnetic moment, with the electron spin either parallel ($|\alpha\rangle$) or anti-parallel ($|\beta\rangle$) to the external field. β denotes the state with the lowest energy. The ratio between electrons in the two states will follow a Boltzmann distribution, with the majority of unpaired electrons in the lower ($|\beta\rangle$) spin state (Atherton 1993).

To induce transitions between the two states, microwaves may be introduced using the magnetic component of a time dependent electromagnetic field of frequency ω_0 applied perpendicular to the external field. Varying the magnitude of the external magnetic field, a *resonance* takes place when the microwave frequency satisfies the *resonance condition*, $\hbar\omega_0 = g\mu_B B_0$, which is a match of the energy separation between the two eigenstates of the unpaired electrons. g is the gyromagnetic ratio of the electron (free electrons have a value of approximately 2.0023). \hbar is Planck's constant divided by 2π and μ_B is the Bohr magneton. The induced transition probability, Γ , between the two states is given by:

$$\Gamma_{\alpha\beta} = \Gamma_{\beta\alpha} = \frac{2\pi}{\hbar} |\langle \alpha | H' | \beta \rangle|^2 \delta(\omega - \omega_0) \quad (7)$$

H' is the perturbed Hamiltonian of the system, incorporating possible magnetic interactions when the spin is in a molecular environment, including electron and nuclear Zeemann terms and hyperfine and quadrupole couplings. Equation (7) states that induced transitions only happen at resonance, i.e., when $\omega = \omega_0$, and the probability of induced transitions from $|\alpha\rangle$ to $|\beta\rangle$ is the same as from $|\beta\rangle$ to $|\alpha\rangle$.

Under equilibrium (without external microwaves), in order for the Boltzmann distribution to prevail, spontaneous transitions are postulated so that:

$$n_\beta W_\beta = n_\alpha W_\alpha \quad (8)$$

n_α and n_β are the number of spins in the two states. W is the probability of spontaneous transitions. The fact $n_\alpha < n_\beta$, implies that $W_\alpha > W_\beta$. The inverse total spontaneous transition probability ($\frac{1}{W_\alpha + W_\beta}$) is the spin-lattice relaxation time, T_1 , which is a measure of the time the spin population uses to recover from a state of non-equilibrium. In addition, a spin-spin relaxation time, T_2 , may be introduced to describe relaxation processes due to spin-spin interactions in the molecular surroundings.

In theory, the resonance conditions will only be fulfilled for a given microwave frequency (cf. eq. 7). Due to $n_\beta > n_\alpha$ net microwave energy will be absorbed by the spin system. Lifetime broadening and small energy perturbations give a resonance curve with

maximum absorption at the resonance frequency. The absorption curve may be of Lorentzian, Gaussian or Voigtian line shape, where the latter is a convolution of the two first (Atherton 1993, Weil *et al* 1994). The Voigtian may be described by the relaxation times, T_1 and T_2 , in addition to the resonance frequency, the microwave power and a term describing inhomogeneous broadening (Lund *et al* 2009).

2.4.2 *Signal detection*

The resonance condition may be achieved by keeping the external magnetic field constant and varying the microwave frequency, or by varying the external magnetic field while the microwave frequency is kept constant. Continuous wave EPR spectroscopy commonly uses the latter method. To detect the absorption of microwave energy, a technique called phase-sensitive detection is applied. An oscillating modulating magnetic field (field strength B_m) is superimposed on the slowly increasing B_0 -field and hence the detected signals will be modulated at the frequency ν_m accompanying B_m . Normally, the modulation amplitude should be significantly smaller than peak-to-peak line width of the EPR signal, and the detected signal will closely approximate the first derivative of the absorption spectrum. Increasing the modulation amplitude leads to a distortion of the detected EPR signal and a line shape which deviates from the first derivative of the absorption spectrum.

2.4.3 *Microwave saturation*

For high microwave field powers, the EPR signal may be saturated, which is due to an overload of the spin relaxation mechanisms in the system studied. Saturation leads to a reduction in the signal increase with increasing microwave power. At increasing microwave power, the detected signal peaks at a given microwave power, and a decrease in the signal is commonly observed at higher powers. Microwave saturation curves for lithium formate irradiated with gamma rays, neutrons, protons and nitrogen ions are shown in figure 5.

2.4.4 EPR Imaging

Using a gradient field encoding technique, it is possible to study the radical distribution within a sample. This is called EPR imaging (EPRI). 1D and 2D EPRI studies have been performed successfully for dosimetric purposes (Gustafsson *et al* 2008a, Kolbun *et al* 2010, Leveque *et al* 2009, Vanea *et al* 2009) but the techniques are still under development.

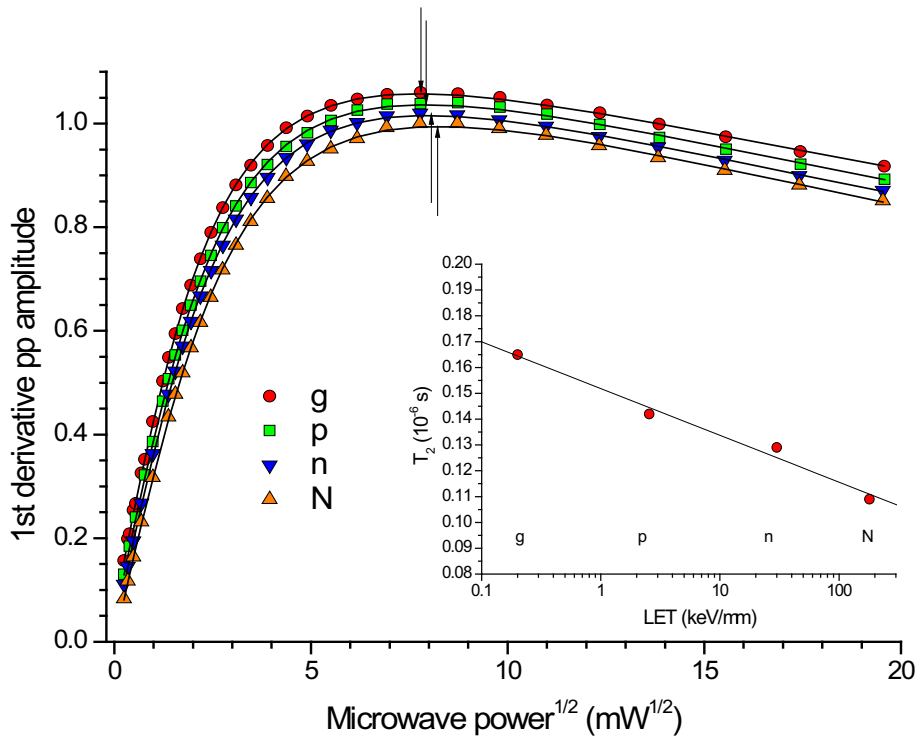


Figure 5: Microwave power saturation of lithium formate dosimeters irradiated with gamma rays (g), protons (p), neutrons (n) and nitrogen ions (N). The figure is from pellets used in paper I and II, and was published by Lund *et al* (2009). T₂ relaxation times derived from the saturation characteristics are displayed in the inset.

3 LITHIUM FORMATE EPR DOSIMETRY

In the search for an EPR dosimeter material more sensitive than alanine, applicable to radiotherapy, lithium formate monohydrate was suggested (Lund et al 2002, Vestad *et al* 2004a, Vestad et al 2003). This material was chosen among ammonium tartrate, salts of formic acids and dithionates by the groups in Oslo and Linköping because of its sensitivity, radical stability, atomic composition close to that of water and simple EPR spectrum (only one, albeit broad, resonance line). Further studies have also investigated and found other advantageous properties compared to alanine, like low energy dependence. This chapter will give an overview of the studies performed on lithium formate EPR dosimetry.

3.1 Material, dosimeter production and stability of EPR signal

Lithium formate EPR dosimeters have been produced manually in all published works. In the papers in this thesis, polycrystalline powder of lithium formate has been pressed into cylindrical pellets of different sizes using a hydraulic, pressure controlled pellet press. Reported dimensions range from the smallest pellets with diameter 3 mm, height 2 mm and weight of approximately 20 mg (paper VI) to the largest dosimeters with diameter 4.5 mm, height and weight approximately 5 mm and 100 mg, respectively (Gustafsson *et al* 2008b).

Dosimeters consisting of pure lithium formate monohydrate have exclusively been used in the current thesis. Studies using paraffin wax (5 – 20% per weight) as binder together with lithium formate have also been performed (Adolfsson *et al* 2010, Antonovic *et al* 2009, Gjøvik 2010, Gustafsson et al 2008b). Regarding the use of binder, the results are not conclusive although the use of a binder is reported to make the dosimeters more robust (Adolfsson et al 2010). Including a binder in the dosimeter could also make the dosimeter more stable to varying environmental conditions. However, accurate Monte Carlo calculations might be more difficult due to the complex composition of powderous mixtures. Furthermore, the water equivalence, with respect to absorption properties, may be altered.

The influence of temperature, humidity and light on the stability of the lithium formate EPR signal is not fully understood, although fading properties have been reported (Fetene 2007, Gjøvik 2010, Gustafsson 2008, Komaguchi *et al* 2007, Vestad et al 2003).

Vestad *et al.* (2003) found no changes in the signal shape or intensity during one week after irradiation and Gustafsson (2008) reported no significant changes in the signal during 28 days. However, Komaguchi *et al.* (2007) reported significant signal fading of pure irradiated lithium formate and lithium formate doped with ^6Li , stored in sealed glass tubes or in air. This experiment was performed in Japan, and the results indicate that high temperature and high humidity could influence radical stability. This may partly be explained by the water content in lithium formate monohydrate ($\text{LiOOCH}\cdot\text{H}_2\text{O}$), which may depend on variations in atmospheric humidity. This is also supported by results of Fetene (2007) and Gjøvik (2010), which report a relatively high loss in EPR signal following high or low humidity and high temperatures. In this thesis a short time (normally within 24 h) from irradiation to readout has been pursued, and the storing conditions have been in sealed containers in the dark at ambient temperature and humidity.

The dependence on irradiation temperature on the EPR signal of irradiated lithium formate was studied in paper III. A slight increase in signal with irradiation temperature was found, and the effect was similar to what was found for alanine dosimeters.

3.2 EPR readout parameters

EPR readout parameters, i.e., filter time constant, sampling time, modulation amplitude, microwave power, scan resolution and amplifying gain, influence the signal amplitude, the signal to noise ratio, the scan time (which is the product of the resolution and sampling time) and the line shape of the signal. Vestad *et al.* (2003) presented the dependence of lithium formate EPR intensity on microwave power for different modulation amplitudes. Also, the dependence of the peak-to-peak line width of the first derivative lithium formate EPR spectrum with modulation amplitude and microwave power was presented in paper I. The experience with EPR reading parameters in the current work has been that each experiment requires an optimized set of parameters, and previous publications have been useful to select appropriate parameters.

For clinical EPR dosimetry, standardized setup, equipment and readout parameters should be employed. For experiments concerning basic research and advanced spectroscopy, the optimal parameters may vary for different issues studied, but they also depend on the spectrometer and cavity adopted. The effective microwave

power in a cavity is normally not the same as the nominal power. In the current thesis, the issues discussed in paper I and II (broadening of EPR resonances), required different and more time consuming readout parameters compared to paper VI, where a dosimetry study with small dosimeters were performed and quick readout times were needed. In paper III, the 'softest' parameters were employed, due to extremely high doses being used.

3.3 LET effects

One of the issues discussed in this thesis was to investigate the feasibility of using lithium formate EPR dosimeters to estimate the linear energy transfer (LET). In others words, it was of interest to look for an "LET fingerprint" in the EPR spectrum. This was mainly discussed in paper I and II, where lithium formate EPR dosimeters were irradiated with neutrons (paper I), protons and nitrogen ions (paper II), all of these particles normally having higher LET than the reference beam quality used, ^{60}Co γ -rays.

The first observation indicating an LET-effect in the form a of broadening of the EPR resonance line of lithium formate for samples irradiated with neutrons compared to x rays was reported by Lund *et al.* (2004). The line broadening was attributed to increased dipolar spin-spin interactions in the dense tracks of high-LET neutrons. However, the effect was only briefly mentioned without showing any data to confirm the statement. In paper I, an increase in the line width of the EPR resonance line following high-LET neutron irradiation was described and quantified. In addition, differences in microwave power saturation characteristics were found between dosimeters irradiated with the low- and high-LET radiation. A more quantitative analysis of the influence of LET on the EPR line width, using a semi empirical line broadening model, was performed in paper II. The line width of the EPR resonance line of irradiated lithium formate as a function of LET, as found in paper II, is displayed in figure 6. Non-linear least squares regression using the semi empirical model is also shown.

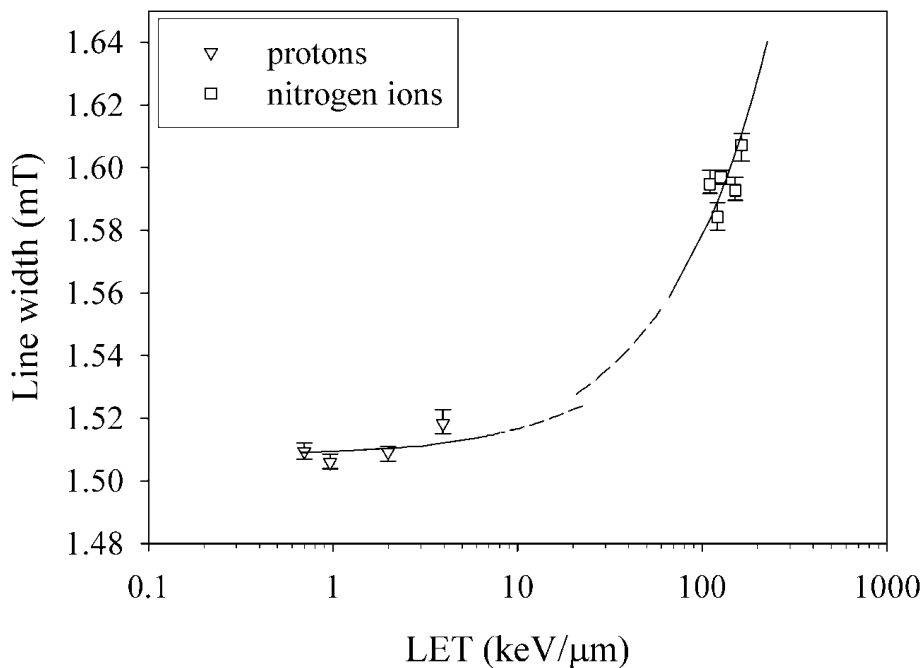


Figure 6: The EPR line width of irradiated lithium formate dosimeters as a function of LET-value of the incident radiation (protons and N-ions), as presented in paper II. Solid and dotted lines are regressions following a semi empirical model, also presented in paper II.

3.4 Modifications of the dosimeter

Different approaches have been tested to modify lithium formate dosimeters to enhance specific properties. This includes mixing lithium formate with other materials, exchanging ^7Li with ^6Li and water with heavy water, and doping of lithium formate with nickel.

Malinen *et al.* (2004) mixed lithium formate and calcium formate and used the composite dosimeter for estimation of x-ray beam qualities. In that work, the different interaction properties and EPR properties of lithium formate and calcium formate were used to determine the effective energy of x-ray beam qualities used.

Lund *et al.* (2004) explored the possibility to use ^6Li enriched lithium formate for dosimetry in mixed radiation fields of photons and neutrons. They found that ^6Li formate was approximately twice as sensitive as ^7Li formate at the same spectrometer settings and x-ray dose. In a mixed photon/neutron field, the ^6Li enriched samples gave 2.5 times

as high signal as regular lithium formate, but a tendency of non-linearity of the dose response was also noted. The increased sensitivity for neutrons was explained by the high capture cross-section of ${}^6\text{Li}(n, \alpha){}^3\text{H}$ reactions as compared to that for ${}^7\text{Li}$.

Komaguchi *et al.* (2007) also used ${}^6\text{Li}$ enriched lithium formate and exchanged the water of crystallization with D_2O , to increase the sensitivity of lithium formate. The impact of heavy water seemed to be negligible, while the ${}^6\text{Li}$ enrichment resulted in an EPR line width of 0.92 mT, which is significantly less than that of regular lithium formate (~1.5 mT). Dosimeters made of ${}^6\text{Li}$ enriched lithium formate were demonstrated to be around 8 times as sensitive as alanine, with a linear dose response from around 0.1 Gy.

Another approach to further increase the sensitivity of lithium formate was proposed by Danilczuk *et al.* (2007). They doped lithium formate with NiCl_2 and demonstrated by this an approximate doubling of the dosimeter response. However, the modifications influence the water equivalence of the dosimeter, and necessitate further investigations before being applied in clinical dosimetry.

3.5 High dose properties

The dose response of lithium formate is shown to be linear from about 0.2 Gy (Vestad *et al.* 2003) to approximately 20 kGy (paper III). In the latter work, a saturation dose (i.e., the dose at which 63% of the saturation level is reached) of 53 kGy was found. For comparison, alanine was found to have a saturation dose of 87 kGy in the same work. Thus, lithium formate appears to be applicable for high dose applications, with a somewhat lower saturation dose than alanine. Furthermore, no difference in EPR signal per dose was found upon irradiating dosimeters using dose rates of 5.5 kGy/h and 0.6 kGy/h to doses between 100 Gy and 10 kGy.

3.6 Energy dependence

The energy dependence of lithium formate is described by comparing the variations in EPR signal when dosimeters are irradiated with clinical beam qualities to that resulting from irradiations with ${}^{60}\text{Co}$ γ -rays (cf. Ch. 2.3). Measured values for lithium formate, F_{Q,Q_0} , found in paper V (medium energy x rays), Vestad *et al.* (2004b) (clinical photons) and paper IV (clinical electrons) are shown in figure 7. The Monte Carlo calculated energy

dependence, H_{Q,Q_0} , from paper IV and V in addition to unpublished results, are also included. Additionally, a recent paper discusses the energy dependence and relative effectiveness for lithium formate irradiated with kV photons (Adolfsson et al 2010), applying air kerma based dosimetry.

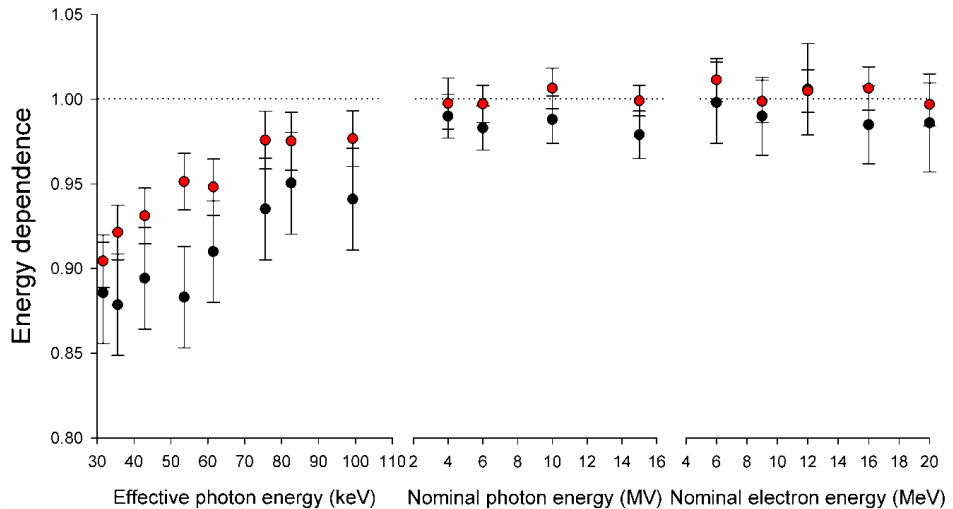


Figure 7: Measured (black dots) and Monte Carlo calculated (red dots) energy dependence of lithium formate dosimeters irradiated with medium energy x rays, clinical photons and electrons. The results for clinical electrons and medium energy x rays are from paper IV and V, while measurements of clinical photons are from Vestad *et al.* (2004b). For the latter beam quality, unpublished Monte Carlo results are included.

3.7 Clinical applications

The first work using lithium formate EPR dosimetry in a clinical setting was published by Gustafsson *et al.* (2008b). Here, lithium formate was used for verification of intensity modulation radiation therapy (IMRT) planning by experimental point measurements. The dosimeters used were cylindrically shaped pellets (diameter 4.5 mm, height 5 mm) with paraffin binder (10% by weight). The authors reported that the method could be used for dose determination within 2.5% uncertainty (coverage factor 1.96) for doses above 3 Gy and dosimeter reading times less than 15 min, while an apparent precision of 0.5% was noted using these dosimeters.

Antonovic *et al.* (2009) used lithium formate EPR dosimetry to perform dose measurements around ^{192}Ir brachytherapy sources. Cylindrical pellets with diameter 4.5 mm and height 4.8 mm were employed and the irradiations were performed using both high dose rate (HDR) and pulsed dose rate (PDR) brachytherapy. Experimentally determined doses were within $\pm 2.9\%$ of treatment planning dose calculations.

The use of lithium formate EPR dosimetry in stereotactic radiosurgery (SRS) was explored in paper VI. In that work, measured 2D dose distributions of an SRS treatment plan were presented and compared to the dose plan. In addition, analyzes of random and systematic errors in the treatment chain were performed. The feasibility of using small lithium formate dosimeters (diameter 3 mm and height 2 mm) and short readout times for 2D clinical dosimetry was demonstrated. A precision of 1.7% was reported.

3.8 EPRI using lithium formate

In two recently published studies (Kolbun *et al* 2010, Vanea *et al* 2009), the use of lithium formate in electron paramagnetic resonance imaging (EPRI) was investigated. Vanea *et al* (2009) used pellets of lithium formate with diameter 22 mm and height 10 mm to measure dose distributions from ^{125}I brachytherapy seeds. Holes were drilled in the centre of the pellets for insertion of the seeds. 2D dose distributions and comparisons with Monte Carlo simulations were presented. In conclusion, lithium formate was demonstrated to have several favourable properties compared to e.g., alanine, but the natural line width of lithium formate (1.5 mT) seemed to be too large compared to the desired spatial resolution.

4 SUMMARY OF PAPERS

4.1 Paper I

Malinen E, Waldeland E, Hole E O and Sagstuen E, **LET effects following neutron irradiation of lithium formate EPR dosimeters.** *Spectrochimica Acta Part A* **63** (2006) 861-869

Lithium formate EPR dosimeters were irradiated with fast neutrons from a ^{238}Pu -Be source, and the EPR signal was compared to that of dosimeters irradiated with ^{60}Co γ -rays. The high-LET (neutron) irradiated dosimeters gave EPR spectra with a significant increase (4.4%) in peak-to-peak line width as compared to that from γ -irradiated dosimeters. Additionally, microwave power saturation properties were found to be different for neutron- and γ -irradiated dosimeters. The dependence of EPR acquisition parameters (microwave power and modulation amplitude) on the peak-to-peak line width of the EPR spectrum was also elucidated.

The increase in peak-to-peak line width following neutron irradiation was suggested to originate from increased local radical density following high-LET irradiation. With high local radical density, T_2 relaxation times will be shorter due to increased spin-spin interactions, leading to the observed differences in microwave power saturation properties.

This work was the first to quantitatively show changes in the EPR spectrum following high-LET irradiation of lithium formate dosimeters, although the line broadening was briefly mentioned in an earlier work (Lund et al 2004). It was suggested that the LET effects found could be used as LET “fingerprints” and that these properties could be used for LET determination in beam qualities with an unknown LET value.

4.2 Paper II

Waldeland E, Hole E O, Stenerlöv B, Grusell E, Sagstuen E and Malinen E, **Radical formation in lithium formate EPR dosimeters following irradiation with protons and nitrogen ions.** *Radiation Research* **174** (2010) 251-257

The purpose of this work was to further investigate the LET dependence on the EPR spectrum of irradiated lithium formate. Proton beams having LETs of 0.7-3.9 keV/ μm and nitrogen beams of 110-164 keV/ μm were used to irradiate lithium formate dosimeters, and the resulting EPR spectra were compared to those for γ -irradiated dosimeters (LET 0.2 keV/ μm). Track structure theory and modelling of detector effectiveness was used to predict the detector response as a function of the LET of the incident beam.

An increased peak-to-peak line width and reduced relative effectiveness with increasing LET value of the incident beam were found, although the range of LET values and types of particles were limited. The reduced relative effectiveness with increasing LET was explained by an increasing number of recombinations due to higher local ionization density. The increased line width was explained by increased local radical density, as in paper I, resulting in increased dipolar intra-track spin-spin relaxation following high LET irradiation.

4.3 Paper III

Waldeland E, Helt-Hansen J and Malinen E, **Characterization of lithium formate EPR dosimeters for high dose applications – comparison with alanine.** *Radiation Measurements* **46** (2011) 213-218

This work comprised lithium formate and alanine dosimeters, and the main goal was to investigate high dose properties of lithium formate dosimeters and to compare these properties with those for alanine.

Dosimeters were irradiated to doses from 100 Gy to 100 kGy, and the EPR response was evaluated. An exponential rise to maximum function was fitted to the experimental

data, and the D_0 -value¹ (Katz 1978, Rotblat & Simmons 1963) was extracted. The EPR signal was also studied for different irradiation temperatures from 11°C to 40°C and two different dose rates (5.5 kGy/h and 0.6 kGy/h).

Using the peak-to-peak value of the first derivative EPR spectrum as dose indicator, saturation doses (D_0) of 53.5 kGy and 87.1 kGy were found for lithium formate and alanine, respectively. No estimates have previously been reported for lithium formate, while the result for alanine is within the range of reported D_0 -values in the literature. No dose rate effect was observed neither for lithium formate nor alanine. A small dependence on irradiation temperature was seen for both dosimeter materials, with temperature coefficients, that is, the percentage change in dosimeter signal per °C change in irradiation temperature, of 0.154 and 0.161 for lithium formate and alanine, respectively.

An increased line width of the EPR signal with absorbed dose was observed for both dosimeter materials. In contrast to paper I and II, where the line width increase was explained by high *intra* track radical density, this current observations were attributed to high *inter* track radical density when using extremely high doses.

4.4 Paper IV

Malinen E, Waldeland E, Hole E O and Sagstuen E, **The energy dependence of lithium formate EPR dosimeters for clinical electron beams.** *Physics in Medicine and Biology* 52 (2007) 4361-4369

The purpose of this work was to estimate the energy dependence of lithium formate dosimeters irradiated with clinical electron beams. Electron beams with a nominal energy of 6 to 20 MeV were used to irradiate lithium formate pellets in a PMMA phantom. The EPR signal of the dosimeters was compared to that for ⁶⁰Co γ -irradiated dosimeters and the energy responses were thus found. Energy responses were compared to Monte Carlo simulations.

¹ D_0 is the characteristic 'saturation dose' of the detector, at which 63% of the saturation level is reached.

The average energy response for lithium formate was 0.99 ± 0.03 , and the experimental results were in good agreement with those from the Monte Carlo calculations. The influence of the phantom material was studied by Monte Carlo simulations using PMMA, water and polystyrene as the medium in which the dosimeters were inserted. The simulated energy response was virtually independent of phantom material, reflecting both the low energy dependence of lithium formate and the relatively high accuracy of the dosimetry procedure (IAEA 2001) used.

The work demonstrated that lithium formate is nearly independent of electron beam energy for clinical electron beams, which is a clear advantage in clinical dosimetry.

4.5 Paper V

Waldeland E, Hole E O, Sagstuen E and Malinen E, **The energy dependence of lithium formate and alanine EPR dosimeters for medium energy x rays.** *Medical Physics* **37** (2010) 3569-3575

This work is a continuation of paper IV, but for medium energy x rays. Alanine was included for comparison. Eight different x-ray beam qualities were used, with nominal potentials from 50 to 200 kV. The dosimeter response was compared to that for ^{60}Co γ -rays. Experimental energy responses were compared to estimates from Monte Carlo simulations.

Energy responses ranging from 0.89 to 0.94 for lithium formate and 0.68 to 0.90 for alanine were found. Monte Carlo calculations were systematically higher, on average 4% and 6% for lithium formate and alanine, respectively.

In paper IV, good correspondence was found between measured and Monte Carlo simulated energy responses, indicating a relative effectiveness (cf. Equation 4) close to or identical to 1. In contrast, paper V showed a relative effectiveness systematically below unity, indicating a reduced radiation yield for dosimeters irradiated with x rays of medium energy as compared to that obtained from γ -irradiated dosimeters. The results for alanine seemed to be in good agreement with the literature, where both experimental and theoretical works have been performed.

Lithium formate showed less dependence on medium energy x rays than alanine, and it was also indicated that a higher fraction of the radiant energy absorbed resulted in stable radicals in lithium formate compared to alanine (relative to γ -rays). The reduced relative effectiveness was explained by increased ion recombinations following x-ray irradiation, due to higher LET values of the secondary electrons as compared to the LET of γ -rays. However, no line broadening as reported in paper I, II and III were observed.

4.6 Paper VI

Waldeland E, Hörling M, Hole E O, Sagstuen E and Malinen E, **Dosimetry of stereotactic radiosurgery using lithium formate EPR dosimeters**. *Physics in Medicine and Biology* **55** (2010) 2307-2316

The clinical use of lithium formate EPR dosimetry was explored in paper VI, applied to stereotactic radiosurgery. In this work a large number of dosimeters were employed. The size of these dosimeters is the smallest used to date for lithium formate EPR dosimetry. The pellets were placed in a 2D grid in an anthropomorphic head phantom, giving a spatial resolution of 4 mm.

Three replicate measurements were performed with the phantom undergoing a realistic treatment chain of stereotactic radiosurgery. A dose deviation of 2.2% was seen between measurements and dose plan in the central region of the dose distribution and the measured dose profiles were slightly narrower than the planned dose profiles. The systematic and random positioning errors were also calculated. Systematic positioning errors were 1.0 mm and 0.4 mm in the vertical and lateral direction, respectively, and random positioning errors 0.9 mm and 0.5 mm in the vertical and lateral direction, respectively. This is well within recommended limits for stereotactic radiosurgery.

Paper VI demonstrated the feasibility of lithium formate EPR dosimetry in a clinical setting, employing small and sensitive lithium formate dosimeters and fast dosimeter readout. The standard deviation of dosimeter readings was 1.7%, indicating that the precision of these small dosimeters was relatively high in the current work.

5 DISCUSSION OF RESULTS AND OUTLOOK

Dose measurements by ionization chambers and diodes are in many cases the methods of choice for clinical dosimetry. However, offline systems like films, gel dosimetry, TL dosimetry and EPR dosimetry provide useful alternatives. These systems have pros and cons, and may be preferable in different situations. TL-dosimeters and EPR dosimeters are maybe the most similar dosimeters in their physical characteristics, being small rods or pellets which may be inserted into phantoms or used for in vivo dosimetry. However, when coming to water equivalence, interaction properties and sensitivity, there are differences. TL-dosimeter materials like LiF, which is one of the most used TL-materials for clinical purposes, are the more sensitive as compared to EPR materials like alanine and lithium formate. Lithium formate has an effective atomic number, Z , of 7.3 and is the most water equivalent material (Z of water is 7.5) of the dosimeters discussed, while alanine and lithium fluoride have effective Z -values of 6.8 and 8.3, respectively (Nowotny 1998, Vestad et al 2004b). Figure 3 shows that lithium formate has the smallest energy dependence over a wide range of photon beam qualities.

In this thesis, some properties of the lithium formate EPR dosimetry system related to high LET irradiation and high dose applications have been elucidated in addition to the determination of energy correction factors. In addition, one clinical application is presented. However, there are still missing steps on the path of bringing lithium formate dosimeters into routine clinical use.

Papers I and II discussed the shape of the lithium formate EPR signal when the dosimeters were irradiated with high-LET beam qualities (neutrons, protons and N-ions), as compared to the EPR signal following low-LET γ -radiation. Among other topics, the possibility of using the peak-to-peak line width of lithium formate as an LET indicator was addressed. These two papers clearly demonstrate an LET-effect of the EPR signal, but the observed differences between the EPR signal following low and high-LET irradiation were not particularly large (up to 6% increase). Thus, measurements of line widths may not be sufficiently precise for LET determination. However, in paper I and in the paper by Lund *et al.* (2009), the microwave power saturation analysis gave larger differences, especially in the P_0 parameter (microwave power at saturation). Few beam qualities (and LET values) were used in the experiments, due to low accessibility of beam sources and facilities. To

improve or confirm the modelling of detector effectiveness used to predict the detector response as a function of the LET, more beam qualities should be added in future experiments. However, as discussed in paper II, LET alone is not sufficient for explaining the detector effectiveness, as the track structure of the ionizing particles and the cross section for radical formation also play a role. Thus, both the type of particle and the LET value (or kinetic energy) should in principle be addressed when discussing effects from densely ionizing radiation beams.

The measurements of energy dependence in papers IV and V were not performed at a Primary Standards Dosimetry Laboratory (PSDL), and hence the dosimetry has fairly large uncertainties (typically 2-3%). The measurements for electrons were also performed in PMMA, while the recommended measurement medium was water. This issue was discussed thoroughly in paper IV. For more accurate energy correction factors for the beam qualities discussed, measurements at a PSDL should be performed.

In Paper VI, small lithium formate dosimeters were applied. This paper is to our knowledge the first work to perform 2D EPR dosimetry in a phantom using a large amount of dosimeters. The experimental setup may also be used for e.g., the determination of the dose distribution from intensity modulated radiotherapy (IMRT). However, the introduction of EPRI opens the potential for performing 2D or 3D measurements with even higher resolution and the method may add valuable information with respect to measuring dose distributions following high-LET irradiation. In any case, small lithium formate dosimeters may also be relevant for small field dosimetry, where the radiation beams have dimensions of typically less than 1 cm.

For accurate dosimetry, standardized EPR readout parameters should be used, as addressed in chapter 3.2. Further studies should focus on deriving optimal EPR readout parameters for lithium formate EPR dosimetry. The results of this thesis show a relatively high precision in the dosimeter readings (typically 1 - 2%), even though different readout parameters and experimental set-up were applied in the different experiments. Dosimetry studies using standardized readout parameters and set-up are hence anticipated to yield an even higher precision.

There is a lack of studies addressing signal fading of irradiated lithium formate dosimeter and the dependence on environmental conditions. Further manufacturing studies should also be done to improve the dosimeter composition and to elucidate the

impact of binder materials on the signal stability, dosimeter properties and sensitivity. It is also possible that the use of high-LET beam qualities may result in lower radical stability in lithium formate dosimeters as compared to that observed after irradiation with low-LET beam qualities, in analogy with alanine (Hansen & Olsen 1989).

Even though EPR dosimeters presently are rarely used for routine clinical dosimetry due to a rather low accessibility of EPR spectrometers and, to date, low sensitivity of the available clinical dosimetry system (alanine), feasibility studies have been performed (Ciesielski et al 2003, Schultka et al 2006, Wagner et al 2008). The non-destructive readout and the resulting possibility to do cumulative dosimetry during the course of radiotherapy are attractive properties. Also, long-time storage of dosimeters for the documentation of consecutive treatment periods may be relevant. However, other convenient systems for clinical dosimetry are commonly available in most clinics, which reduce the need for EPR dosimetry. In spite of that, lithium formate EPR dosimetry could be a candidate for an independent dosimetry system used for quality assurance, complementary dose measurements to the routine systems and as mail-in dosimeter system for comparisons or as a service to clinics without their own readout equipment. Lithium formate EPR dosimetry could meet the requirements for dosimetry of doses from 0.1 Gy. The combination of high sensitivity and the possibility to make dosimeters of different shapes, in addition to the low energy dependence over a wide range of clinical beam qualities makes lithium formate even more interesting and favourable compared to other dosimetry systems like alanine EPR dosimetry or LiF TL-dosimetry.

In order to apply lithium formate in the dose region relevant to radiation protection (< 0.1 Gy), more work is certainly needed. For this purpose, systematic studies using both the technically most advanced equipment (in particular, microwave bridge, signal channel and cavity system) available as well as more routine equipment, an also optimized readout parameters should be performed for both pure lithium formate and manipulated lithium formate. A relevant issue is for instance to determine the lowest detectable dose. However, chemical and physical manipulations of lithium formate should not alter the other favourable properties of lithium formate (e.g., low energy dependence) to a large extent.

In summary, the results of this thesis show that lithium formate EPR dosimetry is a method which may be used for estimating the LET of an unknown incident beam, for high

dose purposes, as a clinical *in vivo* dosimeter for x rays, electrons, protons and heavier particles and for quality assurance in the clinic. However, more research is needed to assess long term fading and to standardize the method.

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