DOSIMETRIC PROPERTIES OF OPAGIS DRUG: AN EPR STUDY

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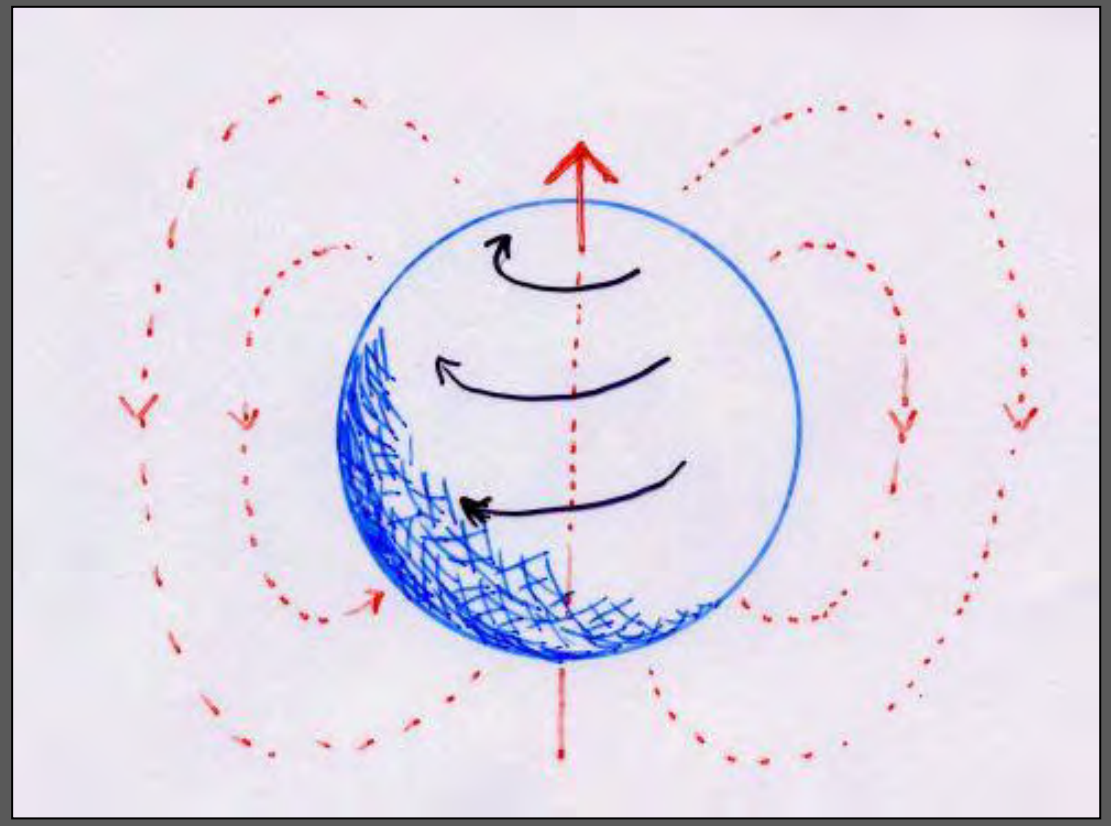
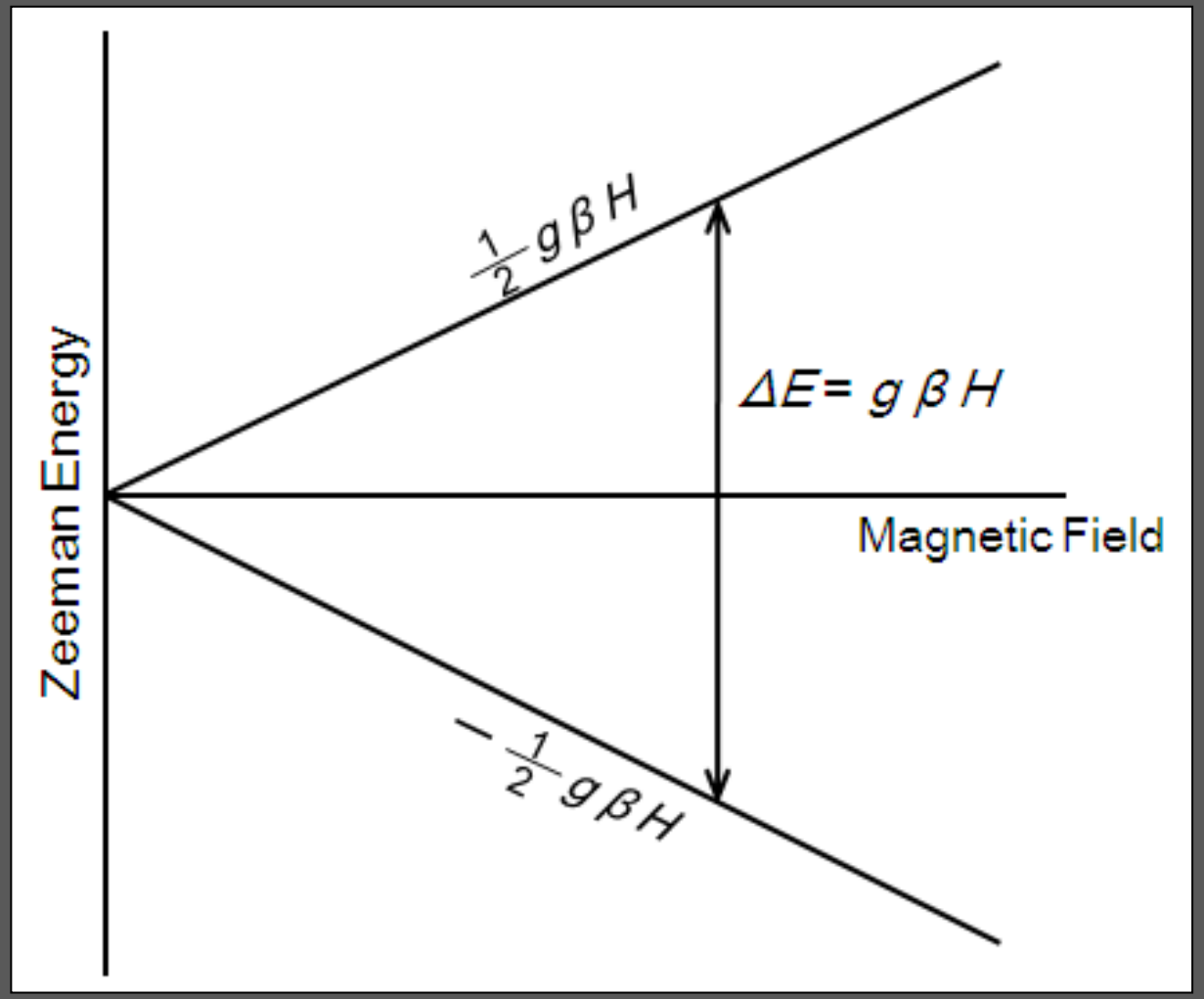
What is Electron Paramagnetic Resonance (EPR)?

- It is used to detect unpaired electrons!



Unpaired electrons are tiny magnets, where the magnetic moments are due to their spins.

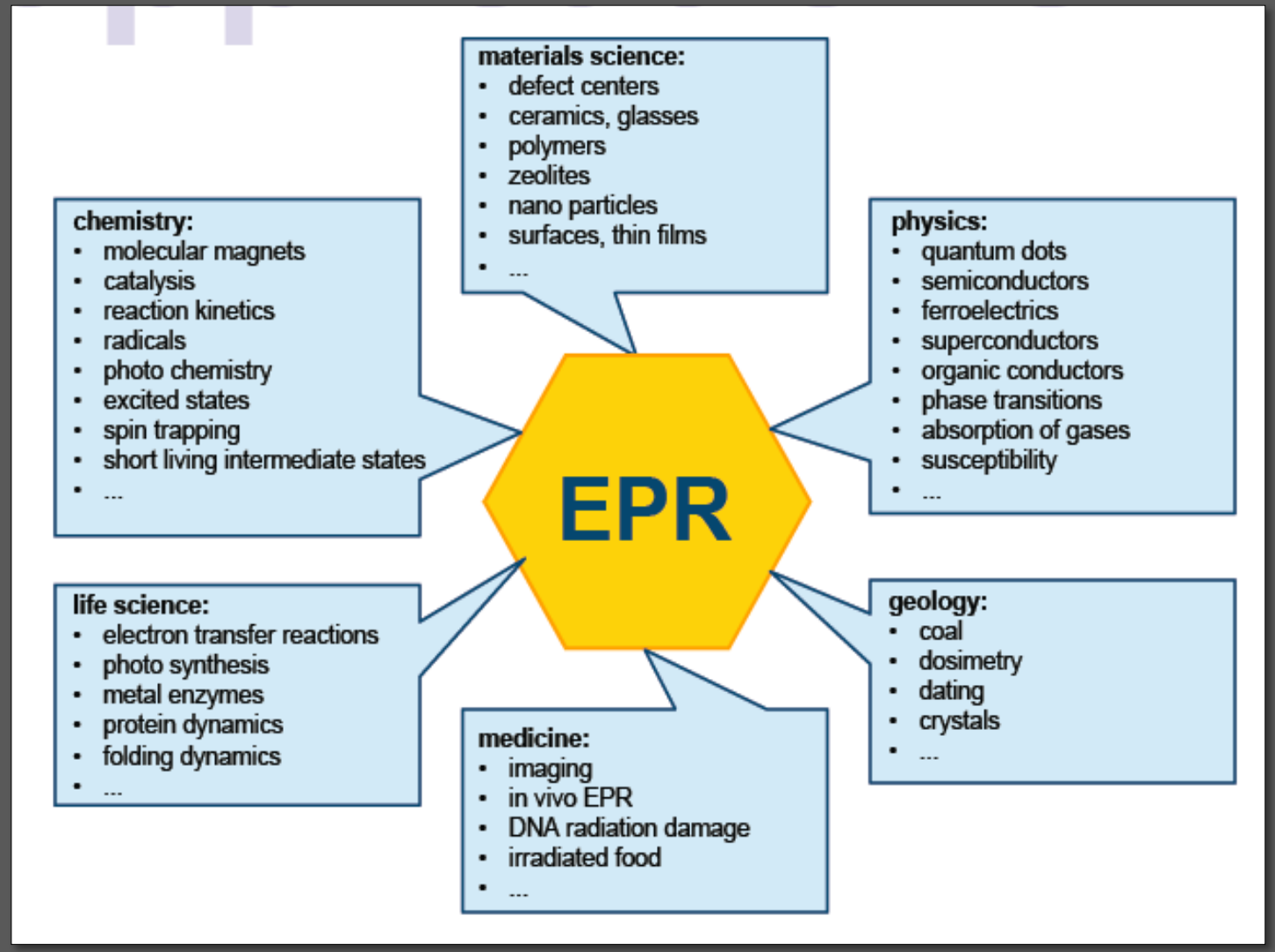
EPR detects the transitions between the energy levels of electron spins induced by electromagnetic radiation in the presence of a static magnetic field.



- The magnetic moments of the electrons become parallel or anti-parallel to the magnetic field.
- Unpaired electrons absorb microwave, the energy of which is equivalent to Zeeman energy splitting.

Resonance Condition
$h\nu = g\beta H$

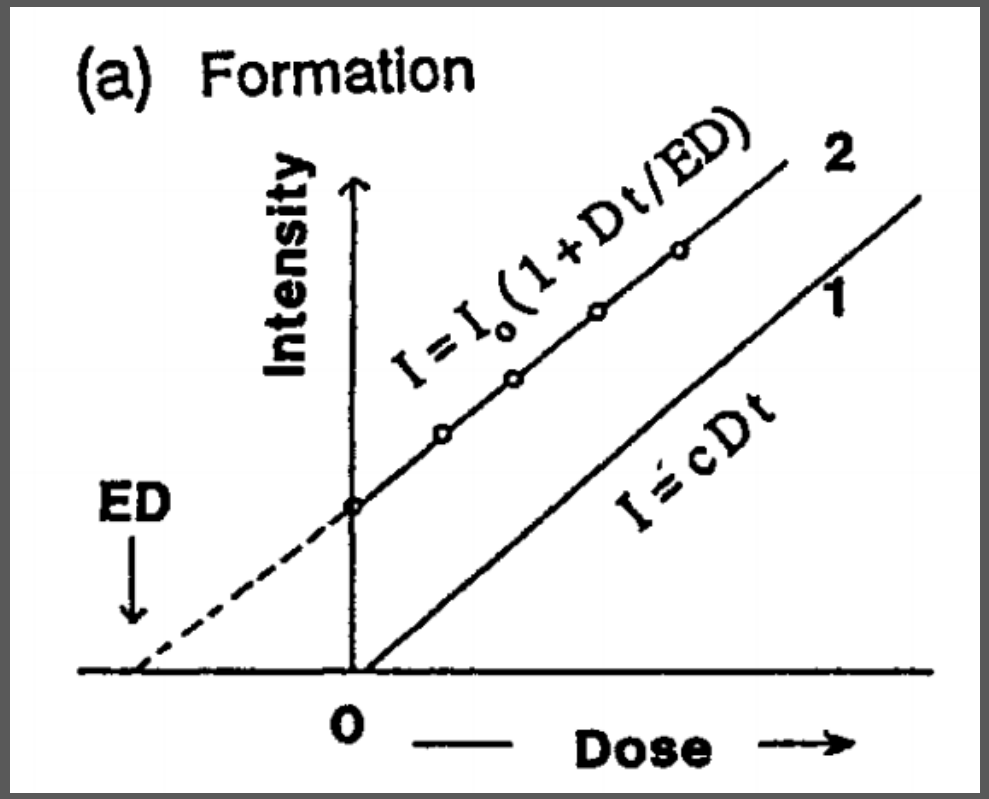
EPR has lots of application fields



- It can be used as a dosimetry for radiation measurements.
- It is a popular technique to investigate dosimetric properties of the materials.

EPR DOSIMETRY ➡ A Retrospective Dosimetry

If paramagnetic centers sensitive to radiation are formed in a material and these centers are stable, the EPR signals of these centers can be used to measure the absorbed radiation dose. These materials are called **EPR DOSIMETERS.**



The EPR signal intensity indicating the density of the magnetic centers is proportional to the radiation dose and irradiation time. The adsorbed dose cannot be determined unless this intensity is scaled to the dose. Based on this principle, a dose-response curve is drawn by measuring the increased EPR signal intensity of the paramagnetic center based on the amount of radiation it receives, and the dose dependency of the EPR signal is determined.

(Ikeya, 1993)

Advantages of EPR Dosimetry

- **Both organic and inorganic materials** can be investigated, thus **tissue equivalent organic materials** can be used as an EPR dosimeter.
- Especially, EPR dosimetry is important for the accident and atomic bomb radiation where the victims do not have a standard dosimeter.
- It is a non-destructive method sensitive to unpaired electron containing materials. Since the EPR centers are not damaged during the measurement, the measurement can be repeated as many times as desired using the same sample.
- Since the EPR is less sensitive to surface phenomena, the particles of the material used do not have to be very small.
- Sample preparation and measurement at room temperature are much easier in EPR.

(Ikeya, 1993; Grün, 1989; Rink, 1997)

An EPR dosimeter must have the properties given below:

- **stable radical (has a long life-time),**
- **contain EPR signals sensitive to radiation,**
- **signal intensity is not dependent on dose rate,**

- small size, easy to use, cheap, non-toxic,
- does not retain moisture,
- easy to pack and suitable for calibration,
- high sensitivity results in dose measurements,
- measurement repeatability,
- not affected by light

Application fields of the EPR dosimeters

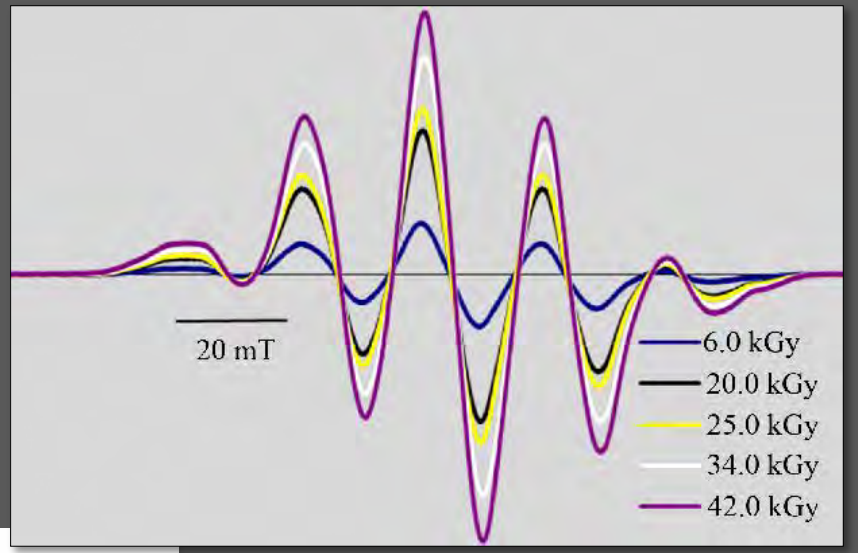
- **Radiation accidents**
- Food irradiation,
- Sterilization,
- Irradiation operations for industrial purposes,
- Nondestructive testing,
- Biological research,
- Agricultural research,
- Radiation therapy

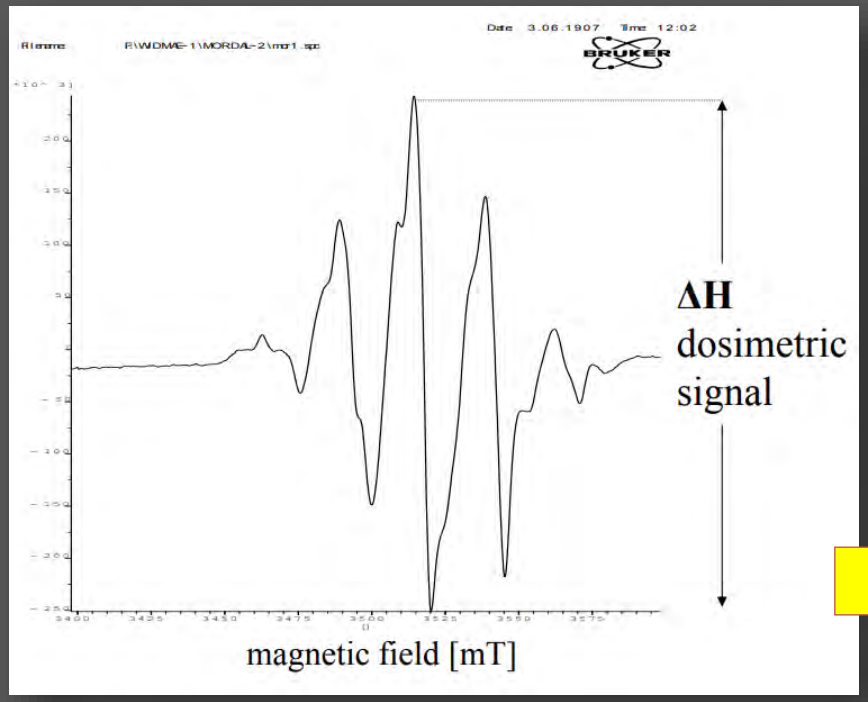
Dosimetric material research is very important for possible nuclear disasters.

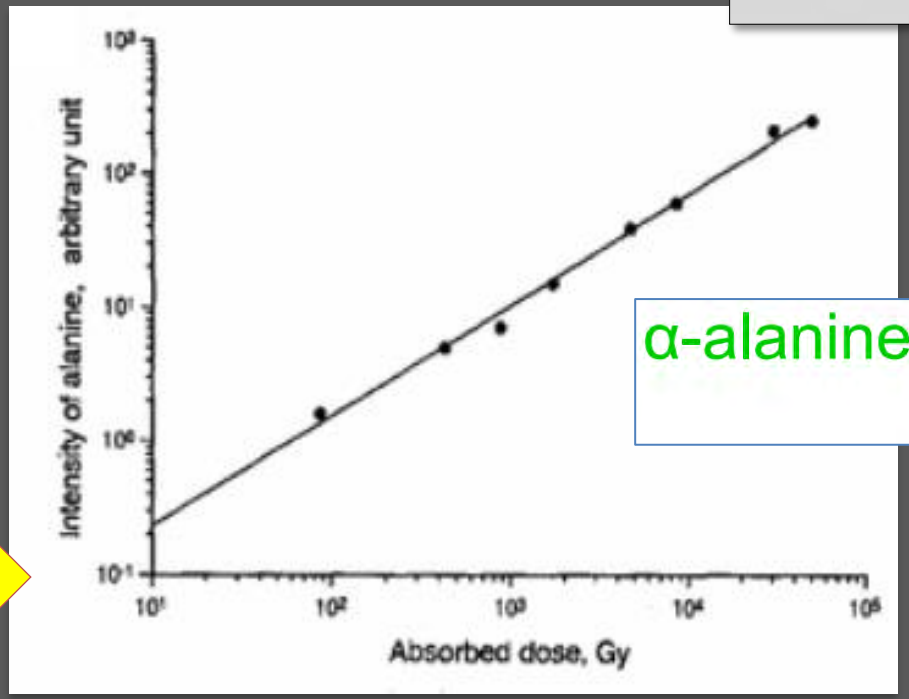
α-Alanine EPR dosimetry

Simple amino-acid ($C_3H_7O_2N$)

- **The EPR technique was first used as "radiation dosimetry" by Bradshaw et al. (1962) for Alanine radicals.**
- The signal intensity of the alanine radical **increases linearly** in the **3 Gy-10 kGy** dose range and can be used as a sensitive dosimeter for this dose region.
- It was later developed and commercialized by embedding samples in binder materials such as paraffin and polyester.







α-alanine: CH_3-$CH(NH_2)$-COOH

dosimetric material

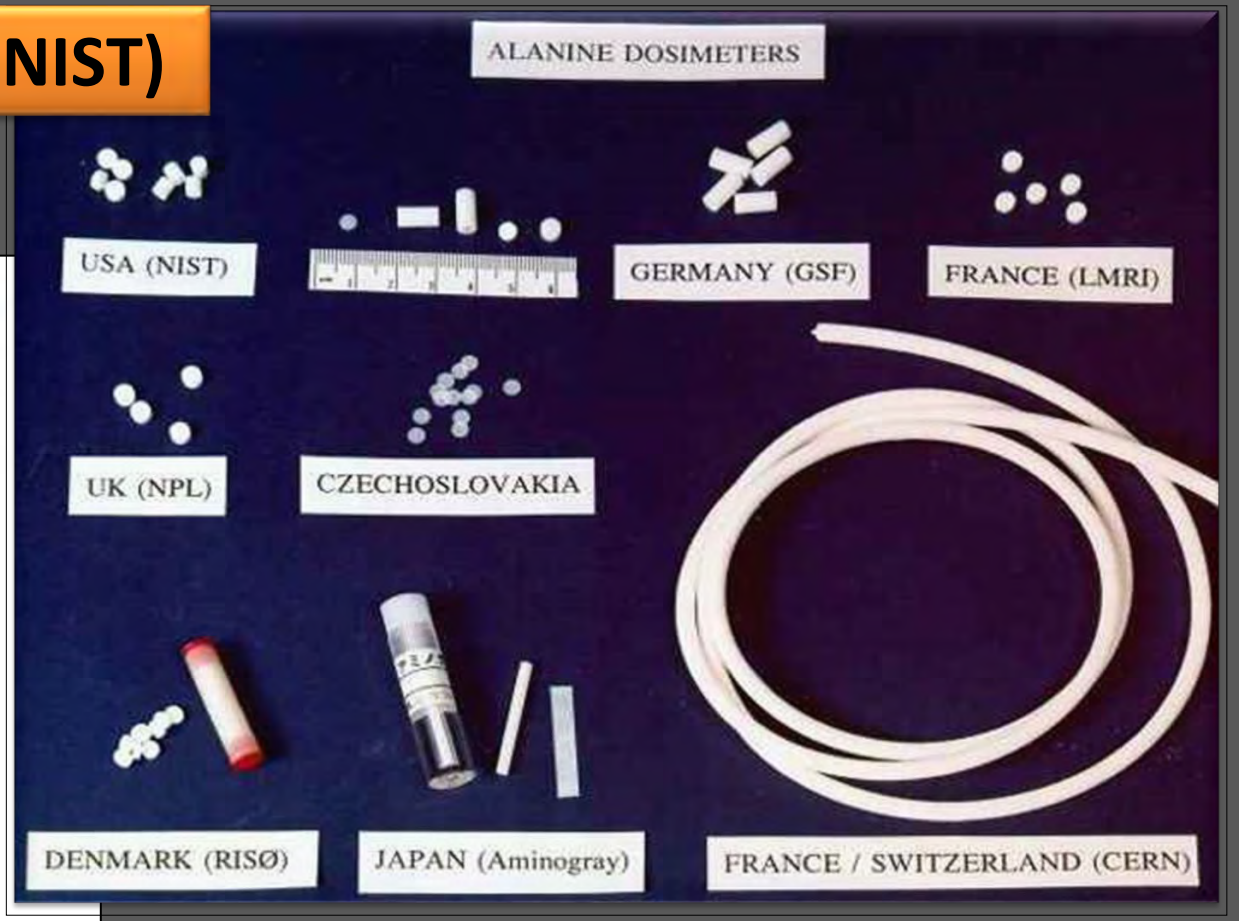
IAEA Training Course, 3-7.12.2007, Warsaw, Zofia Stuglik

organic dosimeter (amino acid)

Advantages of alanine-EPR dosimetry system

- dosimetric signal is stable during very long time (years)
- wide dose detection range (1Gy - 100 kGy)
- linear signal-to-dose dependence (≤ 10 kGy)
- Dosimetric signal is energy and dose rate independent (*gamma and electron beams*)
- accuracy
- non-destructive and fast detection method
- low temperature coefficient of irradiation
- different shapes of dosimeters, also films
- dosimeters are not very expensive
- easy to handle
- non-toxic
- chemical composition of dosimetric material is similar to the chemical composition of organic matter

(NIST)



Human tooth enamel was used as an EPR dosimeter for detection of A-bomb radiation at Nagasaki

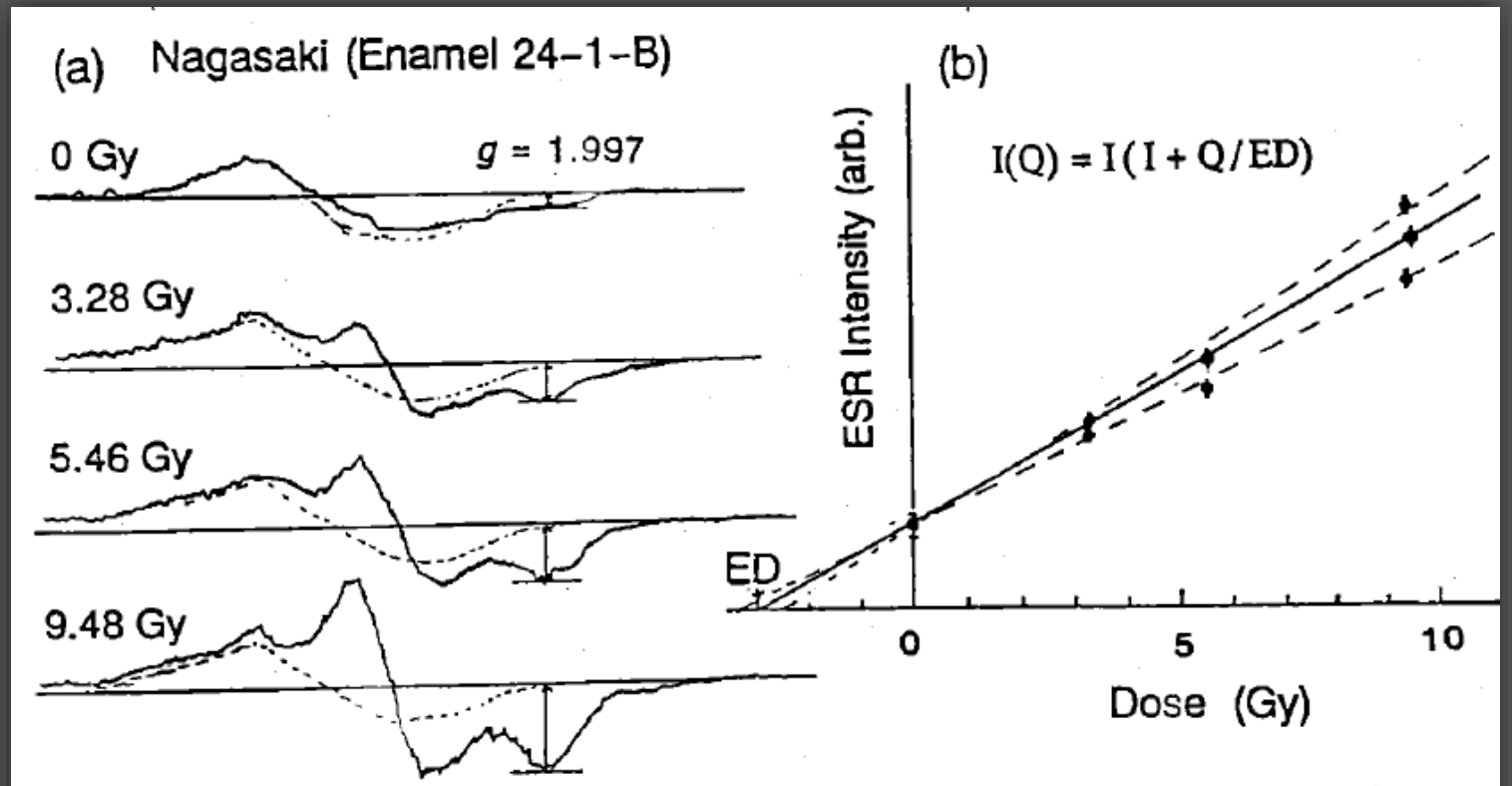
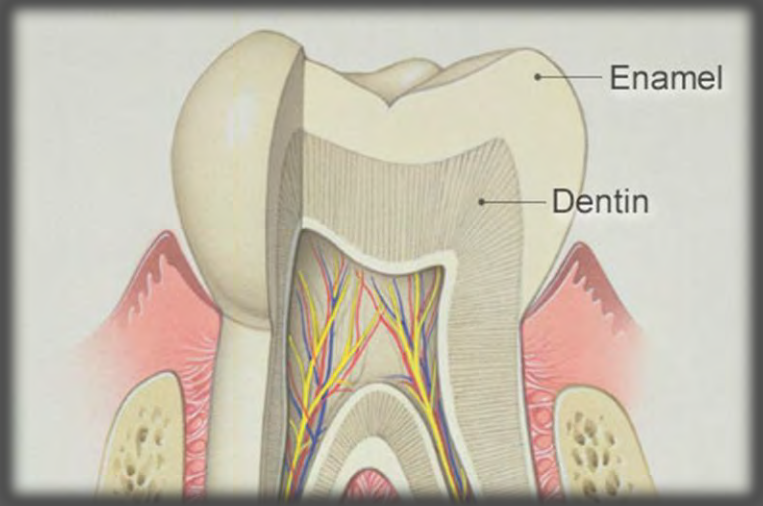


Figure 13.10 (a) ESR spectra of a human tooth by A–bomb radiation at Nagasaki and the enhancement of the signal intensity by γ–irradiation. (b) The A–bomb radiation dose is estimated by a linear extrapolation of the intensity enhancement. A broad signal around $g = 2.0045$ must be subtracted with a computer to determine the low radiation dose of tens of mGy, as in ESR dating of Holocene bones.



Shell buttons were used as an EPR dosimeter for detection of A-bomb radiation at Nagasaki

Japanese Journal of Applied Physics > Volume 23 > Part 2, Number 9

ESR Dosimetry for Atomic Bomb Survivors Using Shell Buttons and Tooth Enamel

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Show affiliations

Motoji Ikeya *et al* 1984 *Jpn. J. Appl. Phys.* **23** L697. doi:10.1143/JJAP.23.L697
Received 30 June 1984, accepted for publication 25 August 1984.

Abstract

Atomic bomb radiation doses to humans at Nagasaki and Hiroshima are investigated by electron spin resonance (ESR) from shell buttons and tooth enamel voluntarily supplied by survivors. A shell button gives a dose of 2.1±0.2 Gy with ESR signals at g=2.001 and g=1.997 while the signal at g=1.997 for the tooth enamel of the same person is 1.9±0.5 Gy. Other teeth show doses from about 0.5 Gy to 3 Gy. An apparent shielding converted to a concrete thickness is given using the T65D calculated in 1965. Teeth extracted during dental treatment should be preserved for cumulative radiation dosimetry.

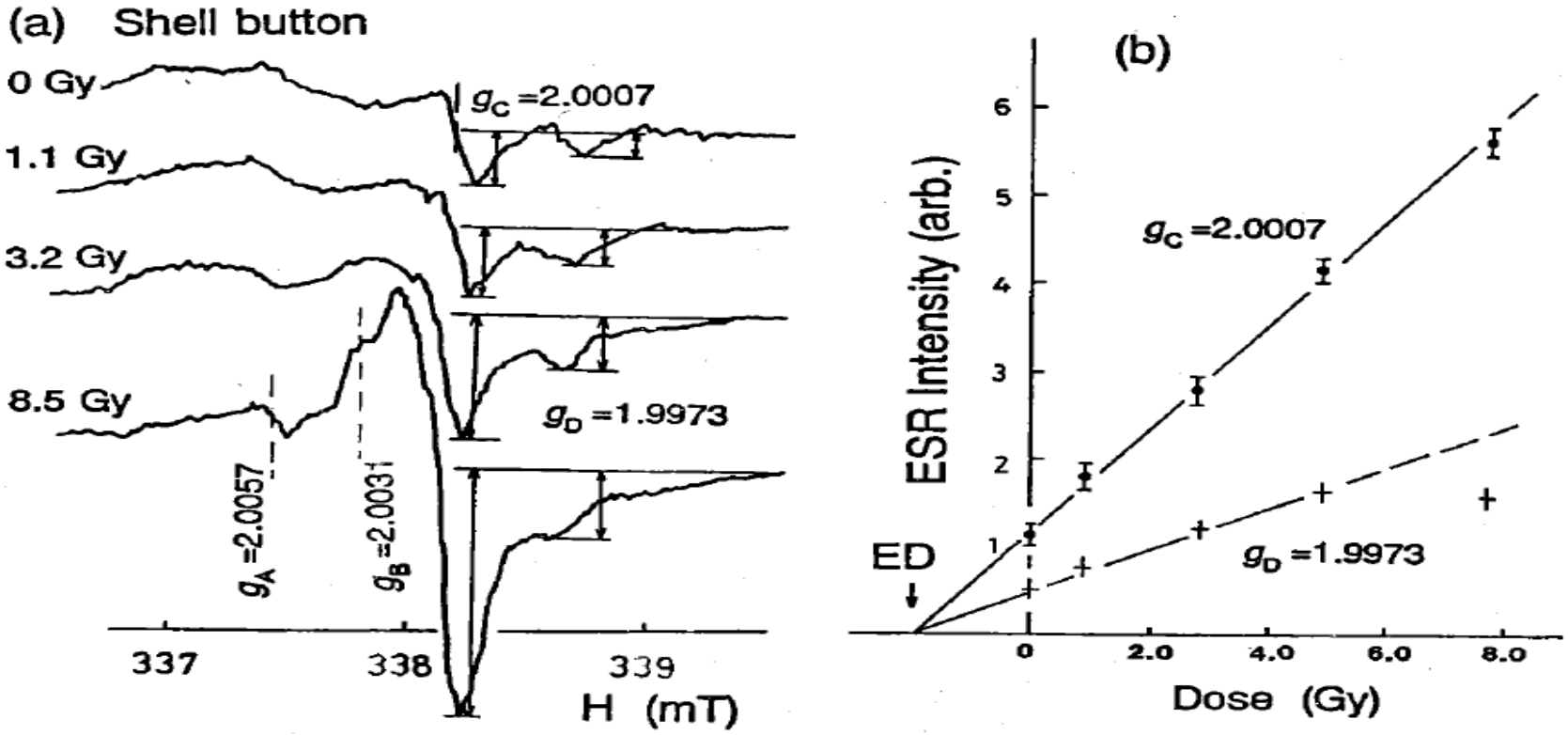

Figure 13.12 (a) ESR spectra of a half piece of shell button supplied by the medical doctor. (b) The enhancement of the signal intensity at g = 2.0007 and g = 1.997 as a function of additive dose. The A–bomb dose equivalent to γ–ray dose from ^{60}Co is 1.9 ± 0.2 Gy (Ikeya *et al*. 1984).

What about Drugs ?

The dosimetric properties of drugs have been the subject of EPR dosimetry studies especially in order to use for the radiation accidents, because it is possible to find them on or near the radiation victims. Also, they can allow rapid and accurate absorbed dose measurements.

The investigated sample is Opagis (30 mg) Drug

We select to investigate the EPR dosimetric properties of **Opagis** because it is a drug widely used for stomach diseases and can be often found near or on the human.

It has lansoprazole as active ingredient.

Excipients: Sugar spheres, mannitol, sodium starch glycolate, magnesium carbonate, povidone K 30, sugar, poloxamer 407, hydroxypropyl methyl cellulose, eudragit L 30 D 55, talc, triethyl citrate, simethicone, titanium dioxide, gelatin.

Each capsule contains 30 mg lansoprazole as enteric-coated granules. Lansoprozole is a benzimidazole derivative and an inhibitor of Na+K+ATPaz enzyme (acid pump), the last step in gastric parietal cell acid secretion. When used concomitantly with an appropriate antibiotic, Helicobacter pylori eradication was achieved. It inhibits mucosal damage associated with non-steroid anti-inflammatory agents such as aspirin.

- Commercial pharmaceutical tablets 30 mg concentration from Mustafa Nevzat pharmaceutical industry were irradiated with ^{60}Co gamma source at a dose range of 10-900 Gy.
- EPR spectra of natural and irradiated samples were recorded by JEOL JesFa-300 EPR spectrometry.

JEOL JES-FA300 X-band EPR Spectrometer

Spectrometer parameters

Frequency: 8.75-9.65 GHz
Sensitivity: 7 x 10^{9} spin / 0.1 mT
Resolution: 2.35 x 10^{-6} T or better
Mode: TE_{011} cylindrical
Q: 18,000 or over
Magnetic field modulation amplitude:
0.0002-2 mT (100 kHz)
0.0002-1 mT (50 kHz)
0.0002-0.2 mT (25 kHz)
Magnetic field scanning width:
0 - (± 500 mT)
Magnetic field scan time:
0.1 s to 12 hours
Magnetic field exchange range:
-10 to 1400 mT

With JEOL Universal Cavity (ES-UCX2)

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Experimental EPR Studies

- Microwave power study at 20 °C → from 0.01 mW to 40 mW
- Dose-response study → from 10 Gy to 700 Gy
- Isochronal annealing study → from 20 °C to 150 °C
- Isothermal annealing study → at the temperatures; 50°C, 65°C, 80°C, 150°C
- Fading study → at room temperature
- Low temperature study → from the temperature 20 °C to -150 °C
- Microwave power study at -150 °C → from 0.01 mW to 7 mW

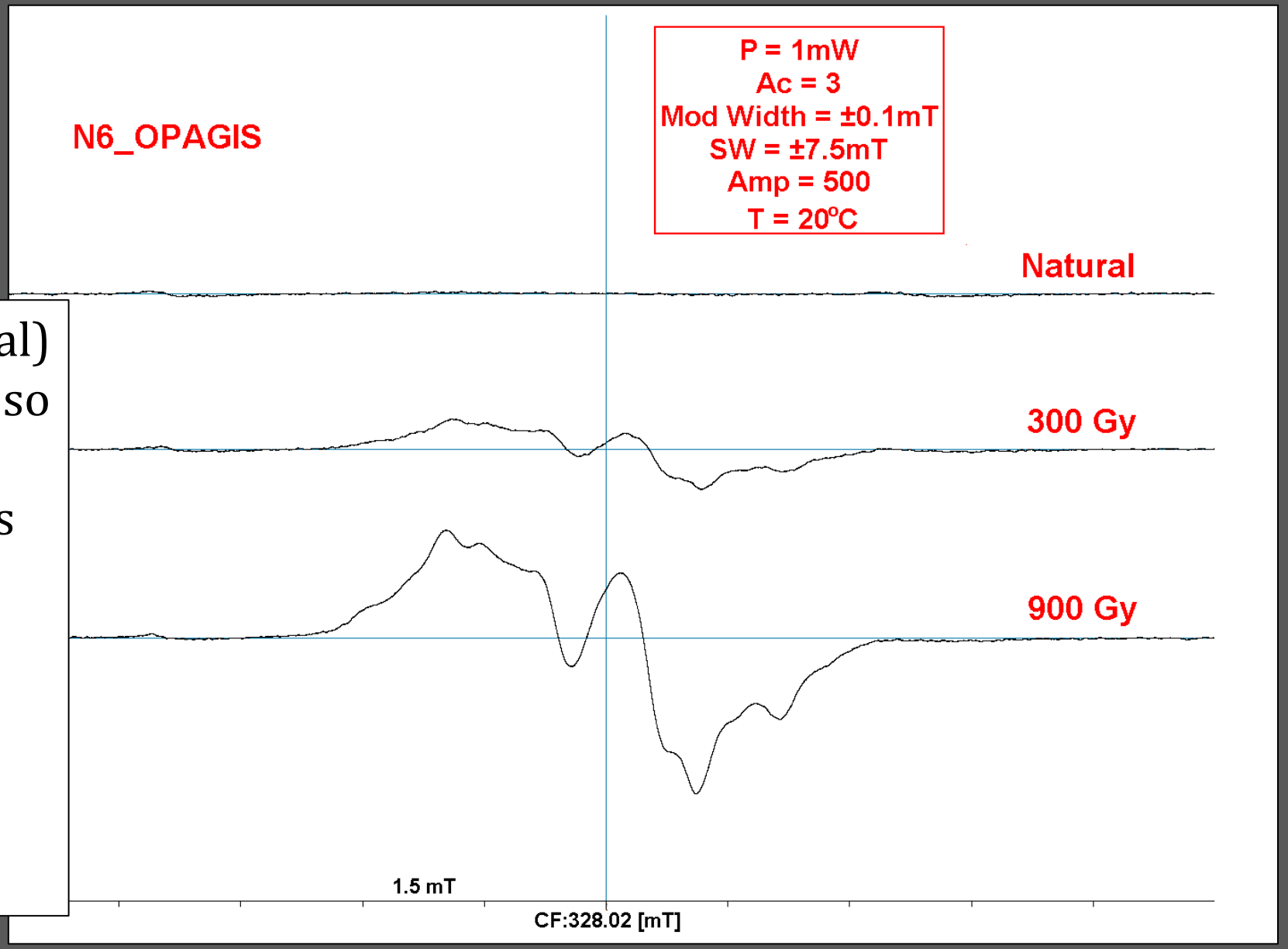
The aim of these studies

- **The main purpose of the study is to investigate the radiation effect on Opagis drug and to determine the dosimetric properties of the radiation induced radical in order to use for radiation accidents.**

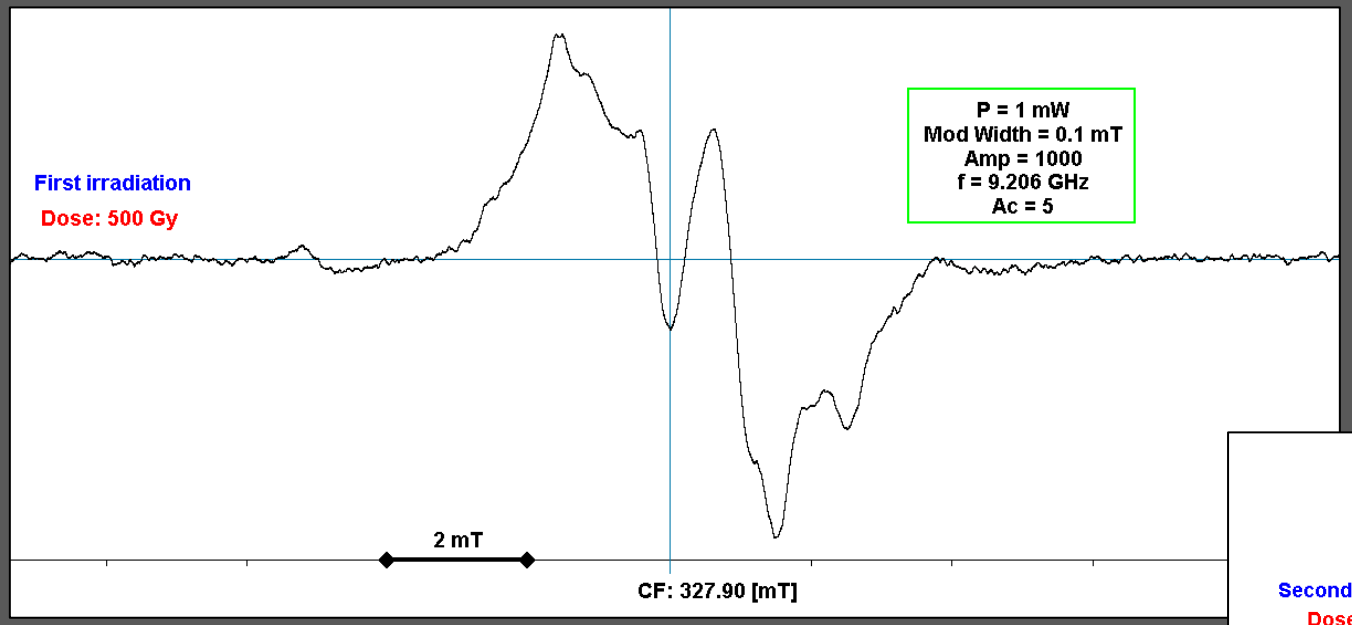
- **Microwave power** and **low temperature studies** were performed to understand if the EPR signals in the spectral pattern are due to only a radical or more than one radical.
- **Dose-response study** was done to determine the radiation dependency of the EPR signals.
- **Isochronal and isothermal annealing studies (at high temperature)** and **fading studies (at room temperature)** are known as **kinetic studies.** These experiments were done to determine the stability of the radiation dependent radical.

Radiation Dose Dependency

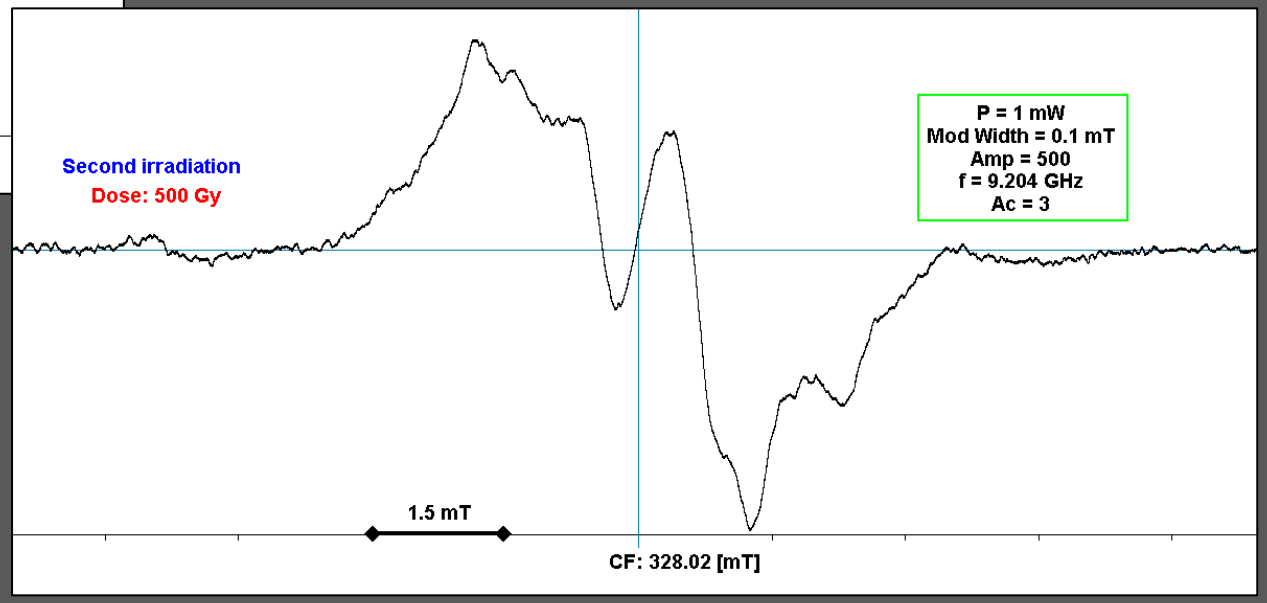
- ✓ Unirradiated sample (natural) did not give any EPR signal, so it is diamagnetic.
- ✓ After irradiation EPR signals which refers to radiation induced radical(s) were observed .
- ✓ The EPR signal intensities increased depending on the applied dose.



EPR spectra of natural, 300 Gy irradiated and 900 Gy irradiated samples



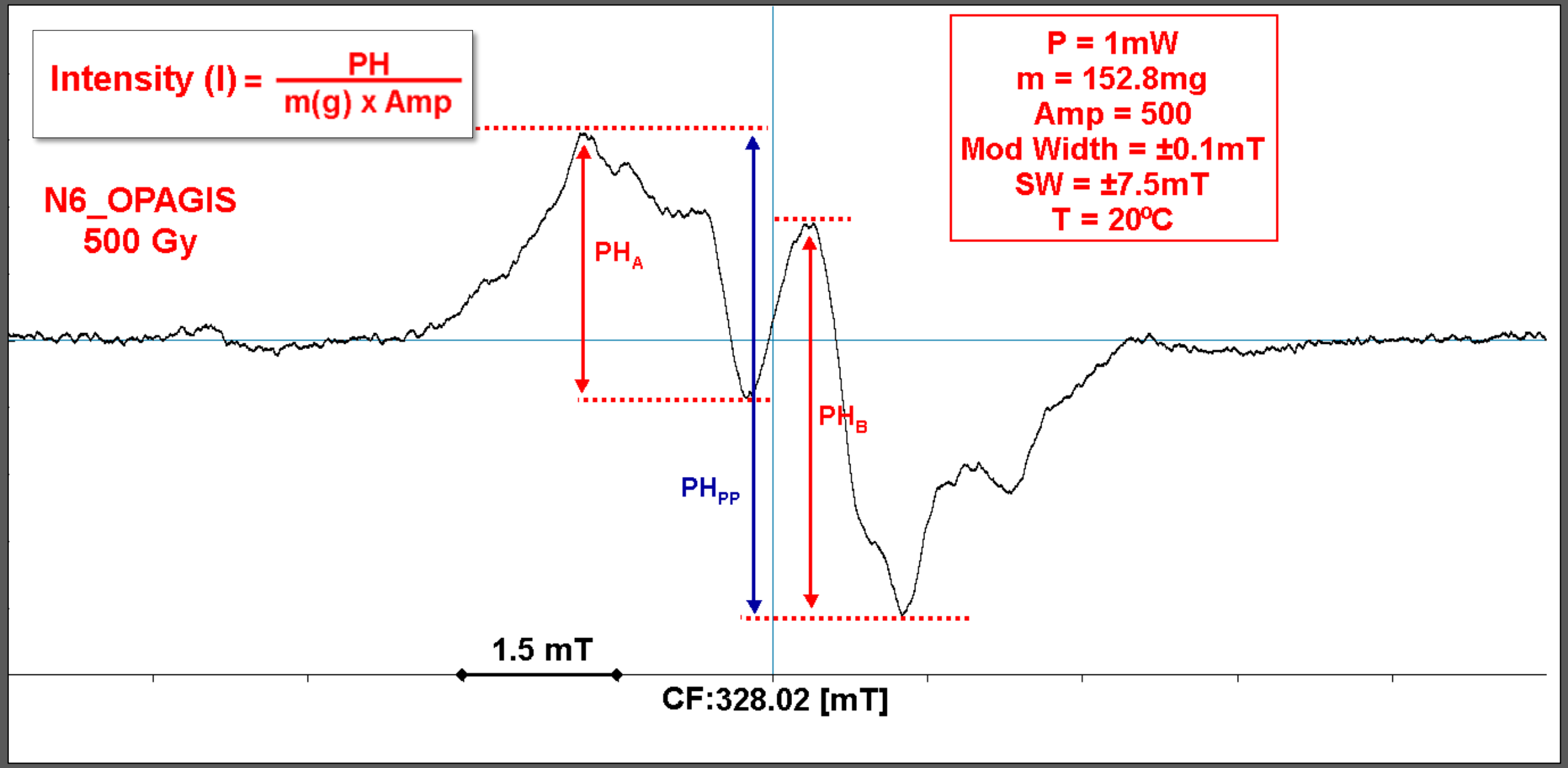
EPR spectrum after first irradiation



EPR spectrum after second irradiation

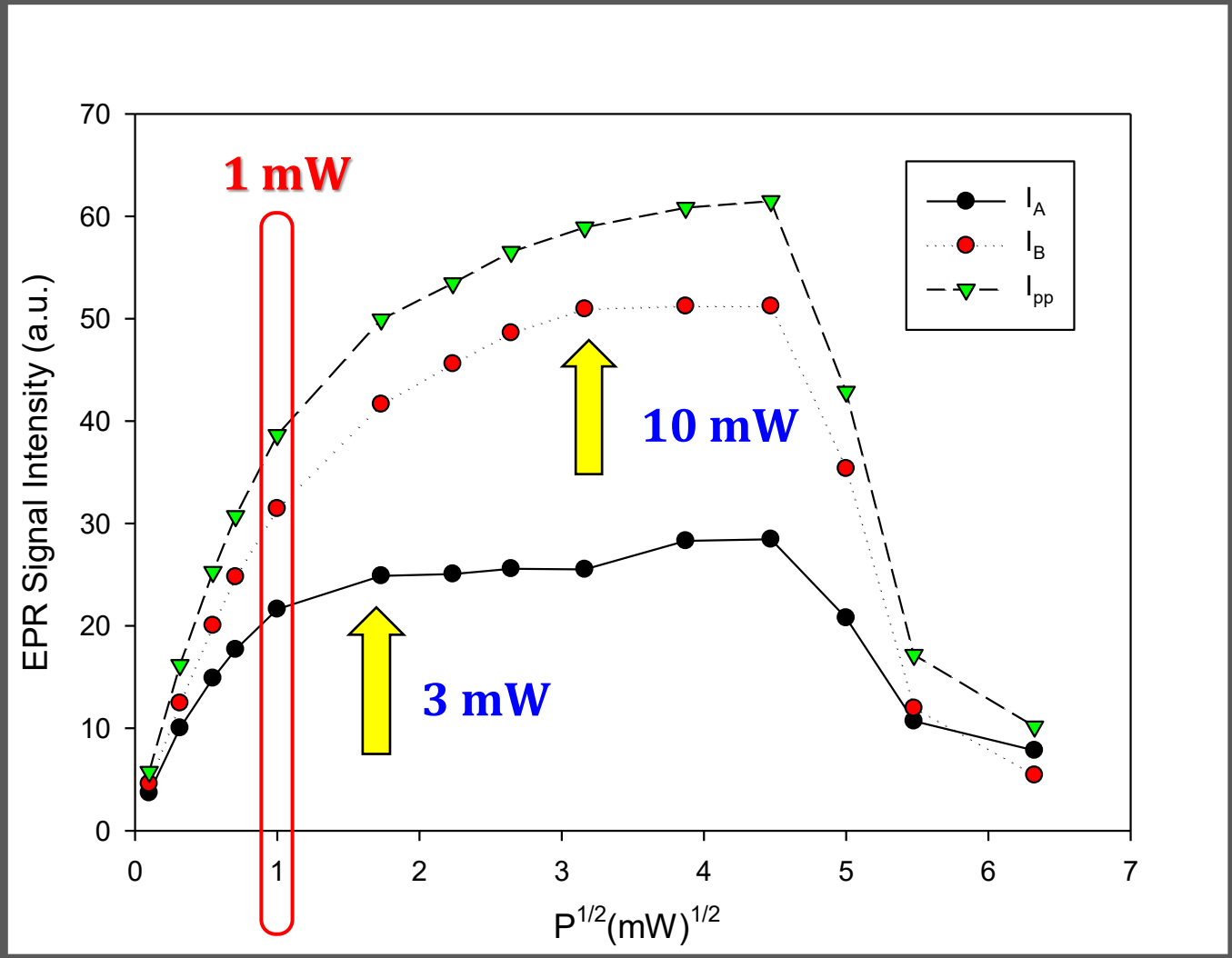
After irradiation at different times, the same EPR spectral pattern have been obtained at the same dose. That is, the radical formed by radiation is the same, so the sample can be used for dosimetric purposes.

EPR Spectrum of 500 Gy irradiated sample
Peak Height Labeling of Signals



Microwave Power Dependency at Room Temperature (T = 20 °C)

- ✓ As seen from the graph, A and B signal have different microwave power dependency.
- ✓ Signal A saturated at 3 mW, while Signal B saturated at 10 mW.
- ✓ Because it was far from the saturation for both A and B signal, we decide to use 1 mW microwave power at other EPR experiments.
- ✓ In addition, the resolution of the spectrum was well at the 1 mW microwave power.



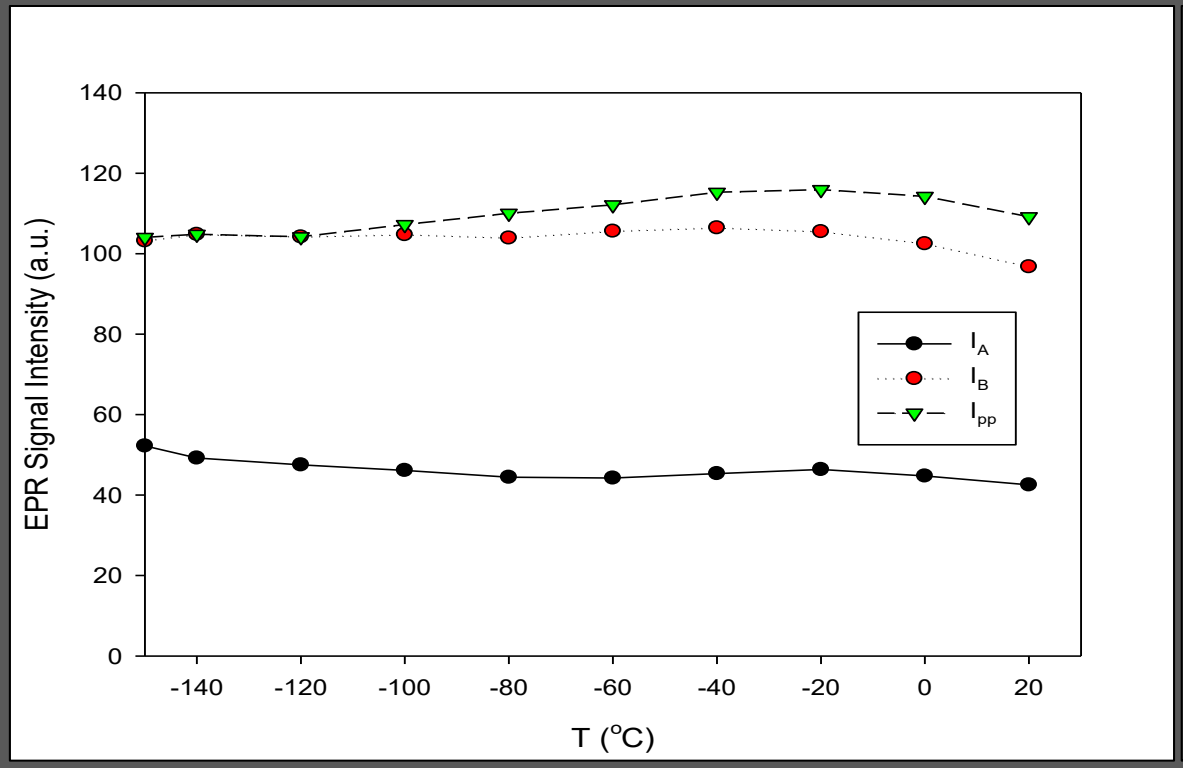
Microwave power dependency graph of EPR signals for 500 Gy irradiated sample.

Low temperature studies from 20 °C to -150 °C

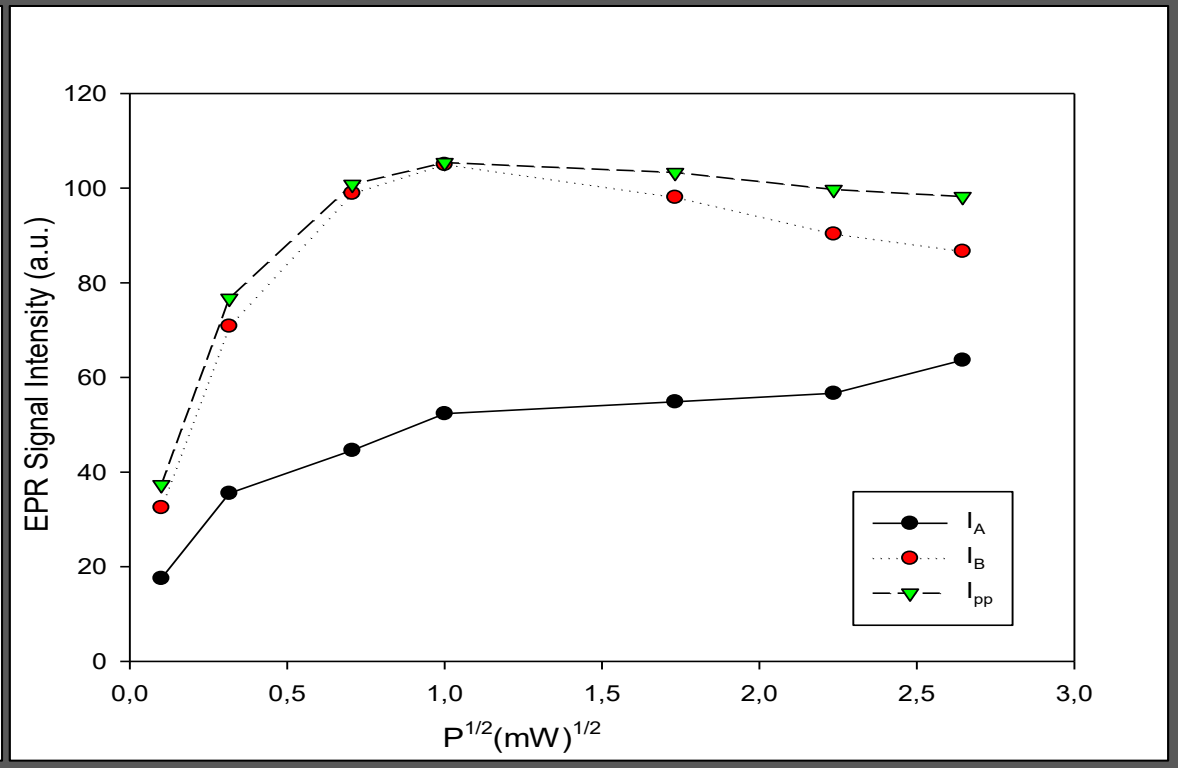
by using JEOL liquid nitrogen variable temperature controller (JEOL/ES-DV4)

- Temperature dependency while going low temperatures
- Microwave dependendency at -150 °C

P = 1mW
T values are from 20 °C to -150 °C



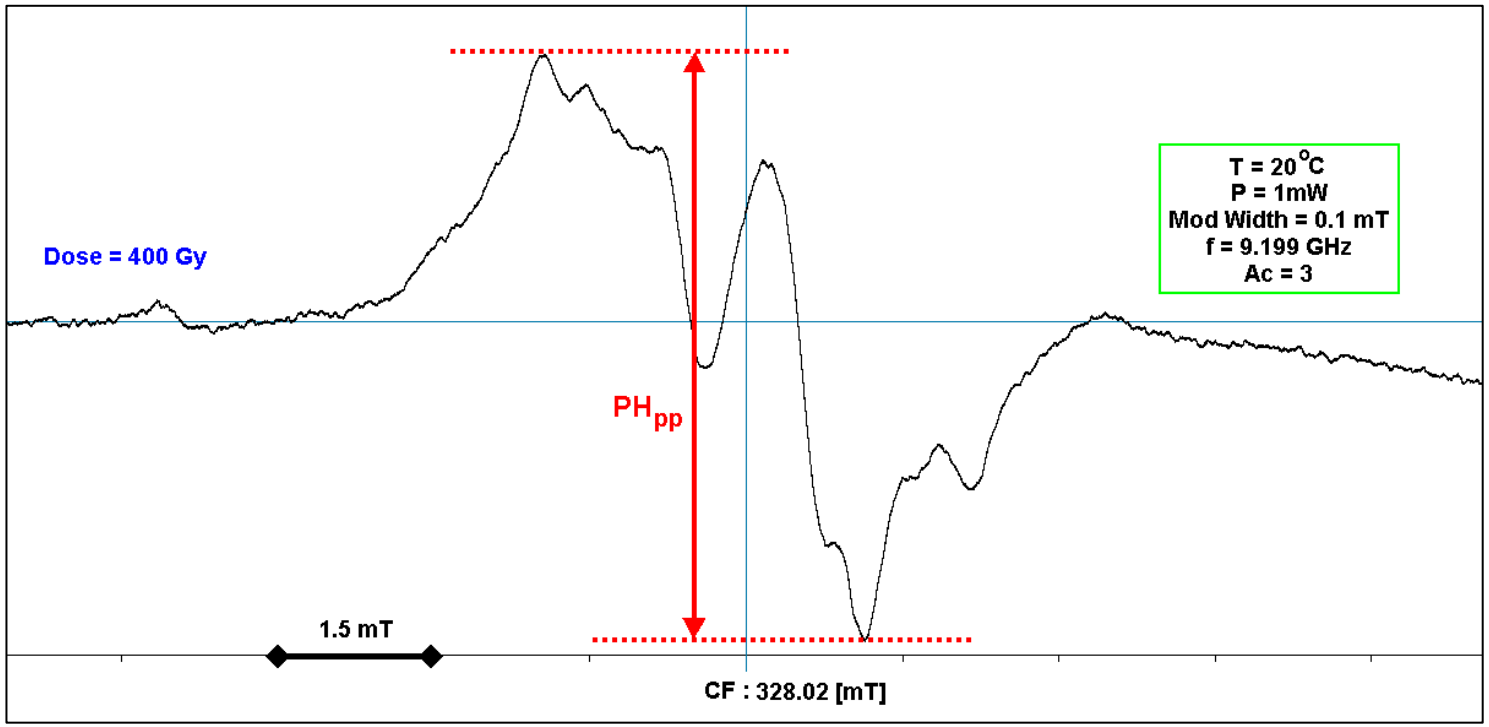
T = -150 °C
P values are from 0.01 mW to 7 mW



For A and B signal, the temperature dependency from 20 °C to -150 °C were nearly same, however the microwave dependency of two signals were different at -150 °C. This confirms that more than one radical is formed in the structure.

It was thought that radiation produced more than one radical, because the microwave dependency at both room (20 °C) and low (-150 °C) temperature were different for the signals A and B.

So, it would be more accurate to consider the peak-to-peak EPR signal intensity (I_{pp}) to construct the dose-response curve.



Dose-Response Study

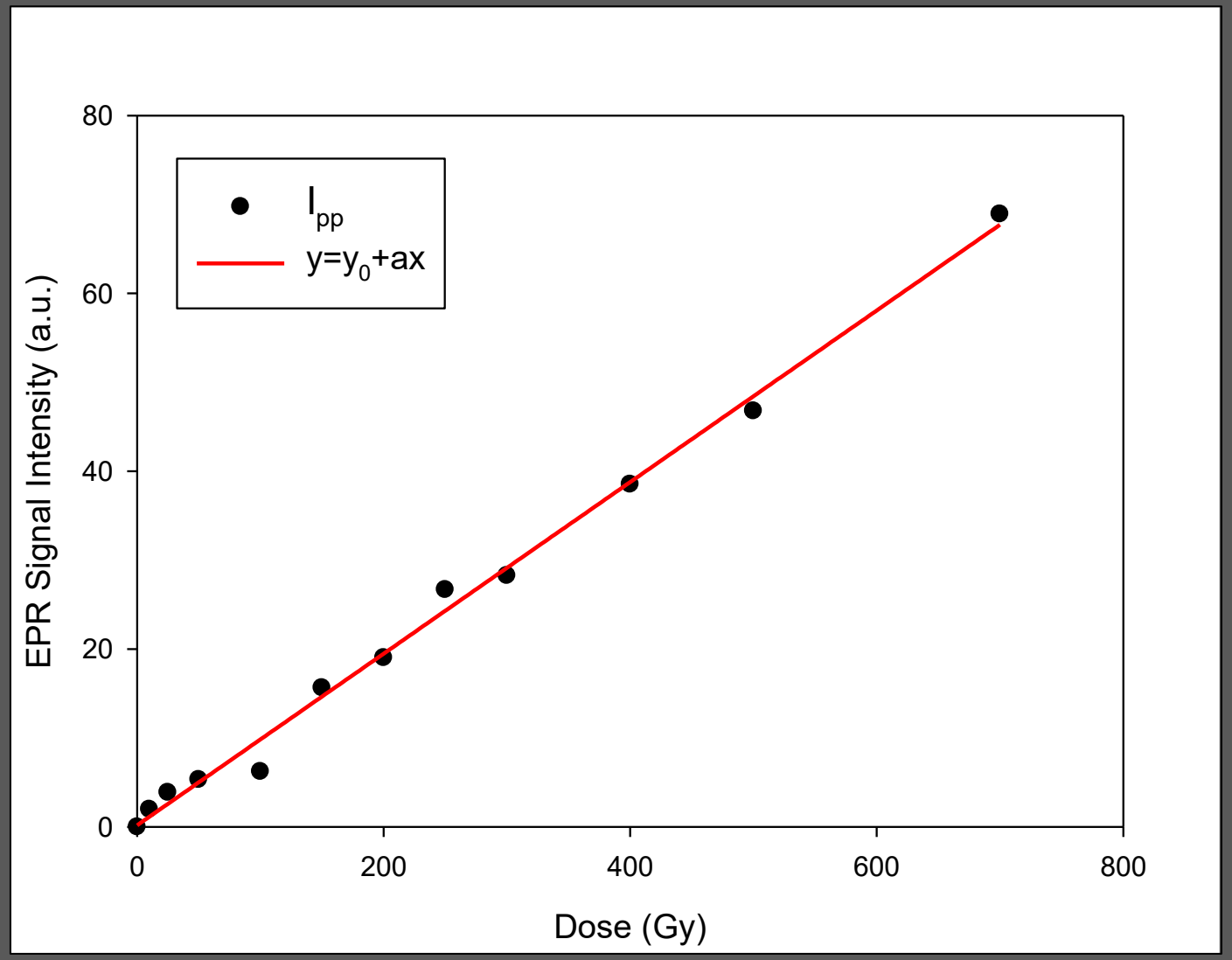
The dose dependency of EPR signal intensity (I_{pp}) was fitted to a linear function in the dose range of 10 Gy to 700 Gy.

$$y = y_0 + ax$$

$a = 0{,}0965 \pm 0{,}0023$

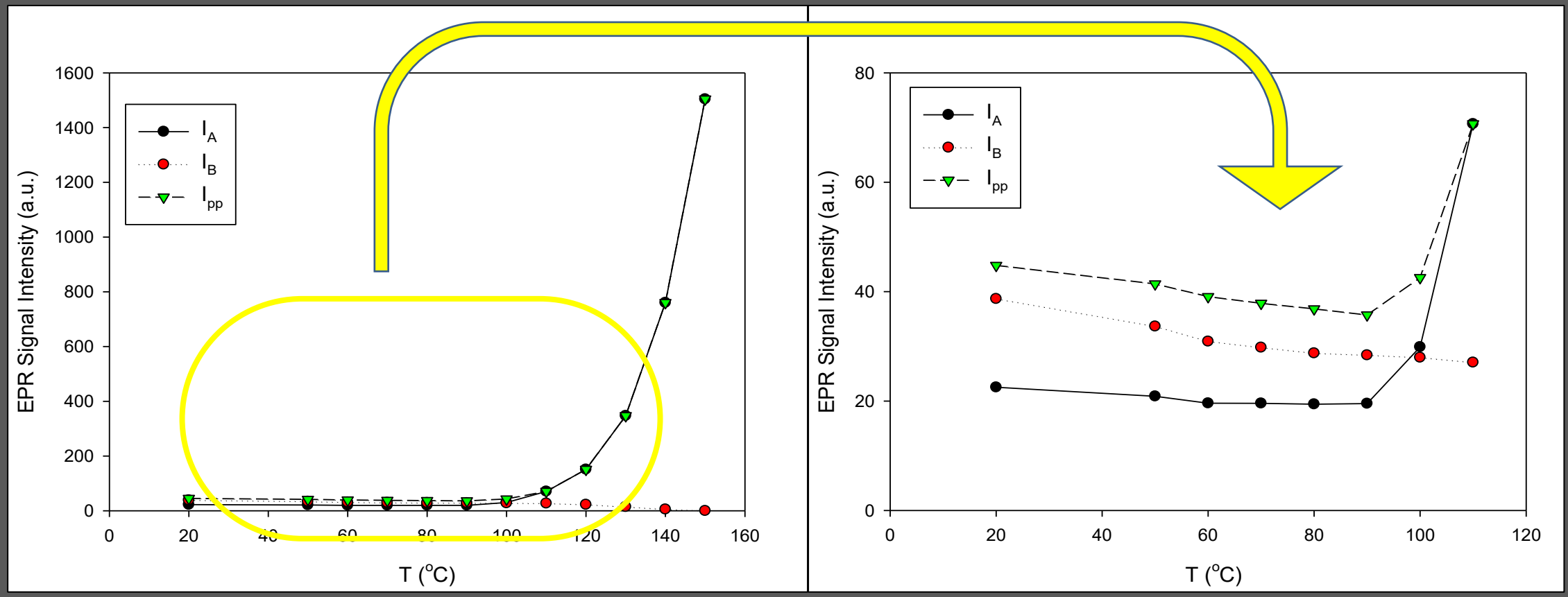
$R^2 = 0{,}9945$ **correlation coefficient**

Minimum Dedectable Dose (MDD) $\cong$ 3 Gy

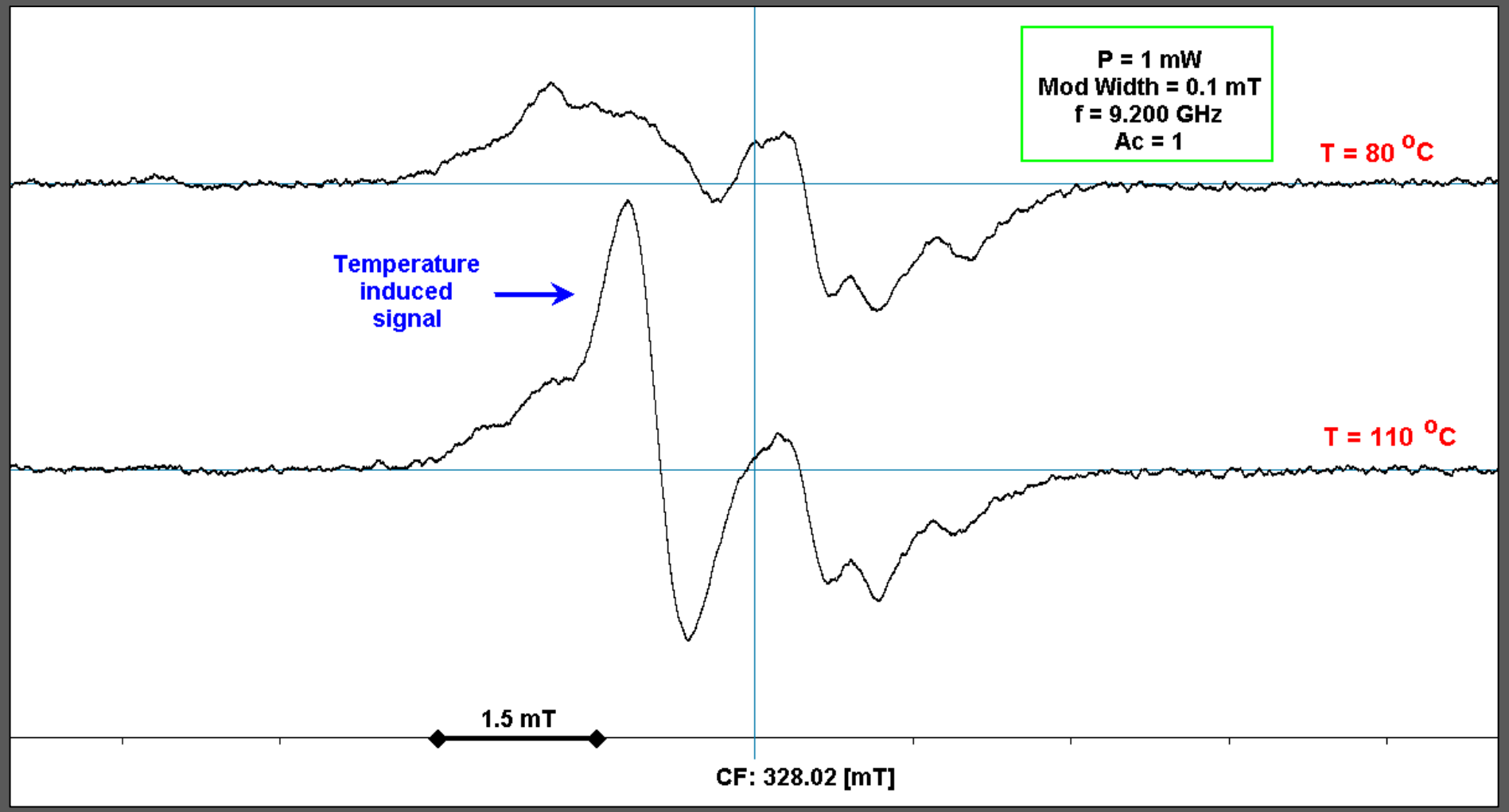


Dose-response curve of peak-to-peak EPR signal

Isochronal annealing (from 20 °C to 150 °C) (t = 3 min) for 600 Gy irradiated sample

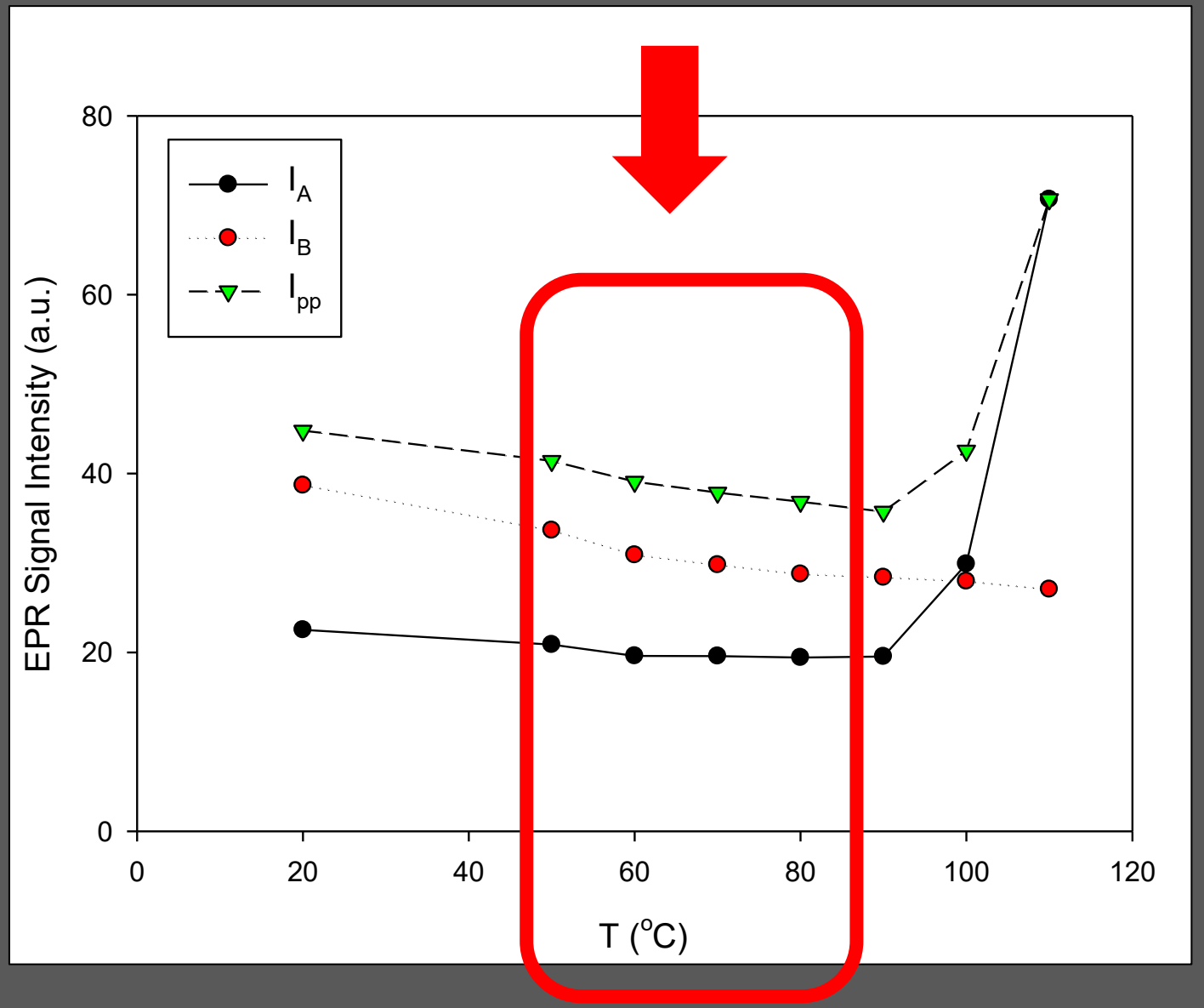


It is observed that as the temperature increases, the signal generated by the radiation decreases, but a new EPR signal is formed in the magnetic field region where the A signal is located.

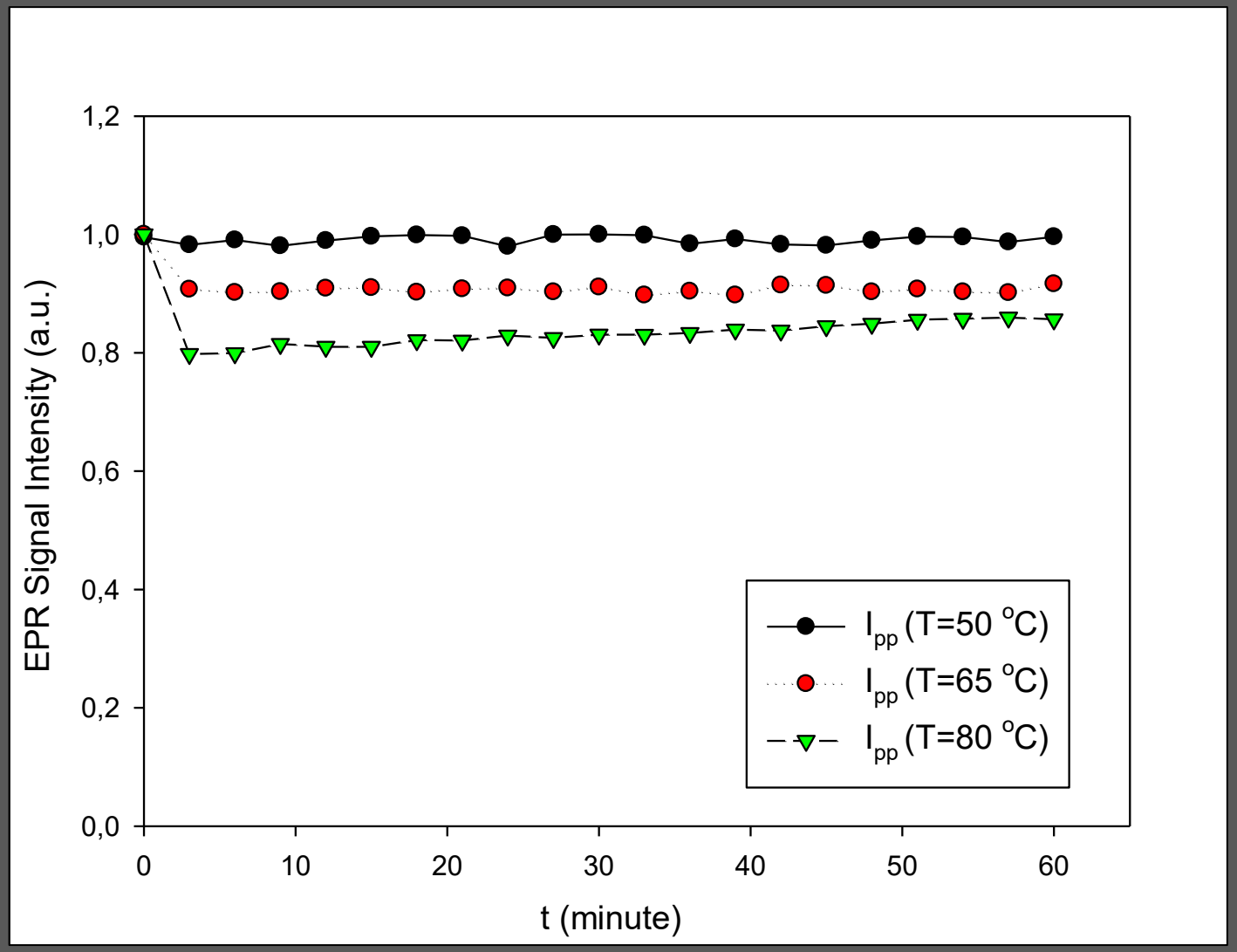

P = 1 mW
Mod Width = 0.1 mT
f = 9.200 GHz
Ac = 1
T = 80 °C
Temperature induced signal
T = 110 °C
1.5 mT
CF: 328.02 [mT]

Isothermal kinetic studies at 50 ºC, 65 ºC, 80 ºC

- The temperatures used in isothermal experiments were determined from the isochronal experiments.



Isothermal decay curves of peak-to-peak normalized EPR signal intensities versus to time for 50 °C, 65 °C and 80 °C temperatures

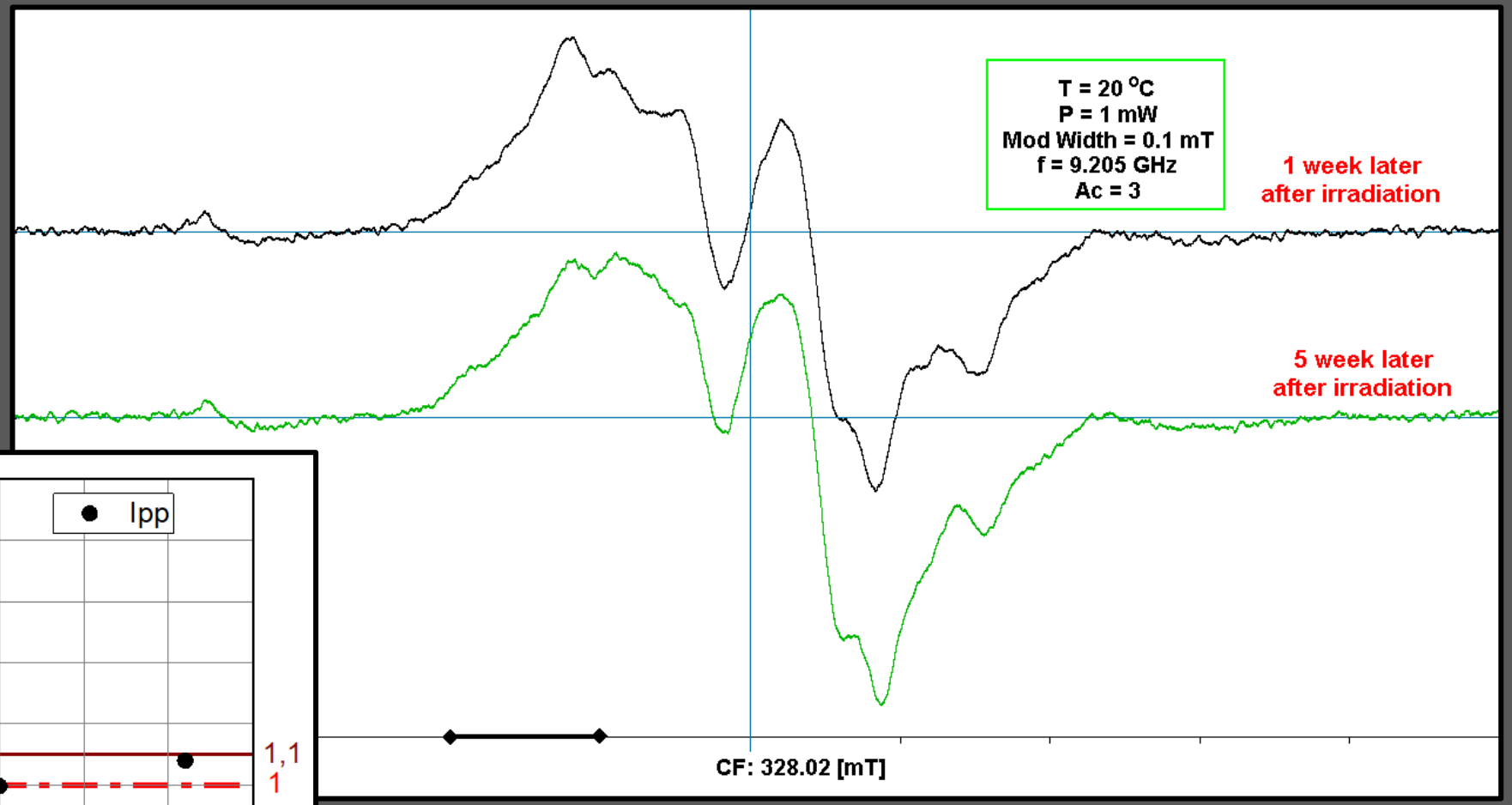


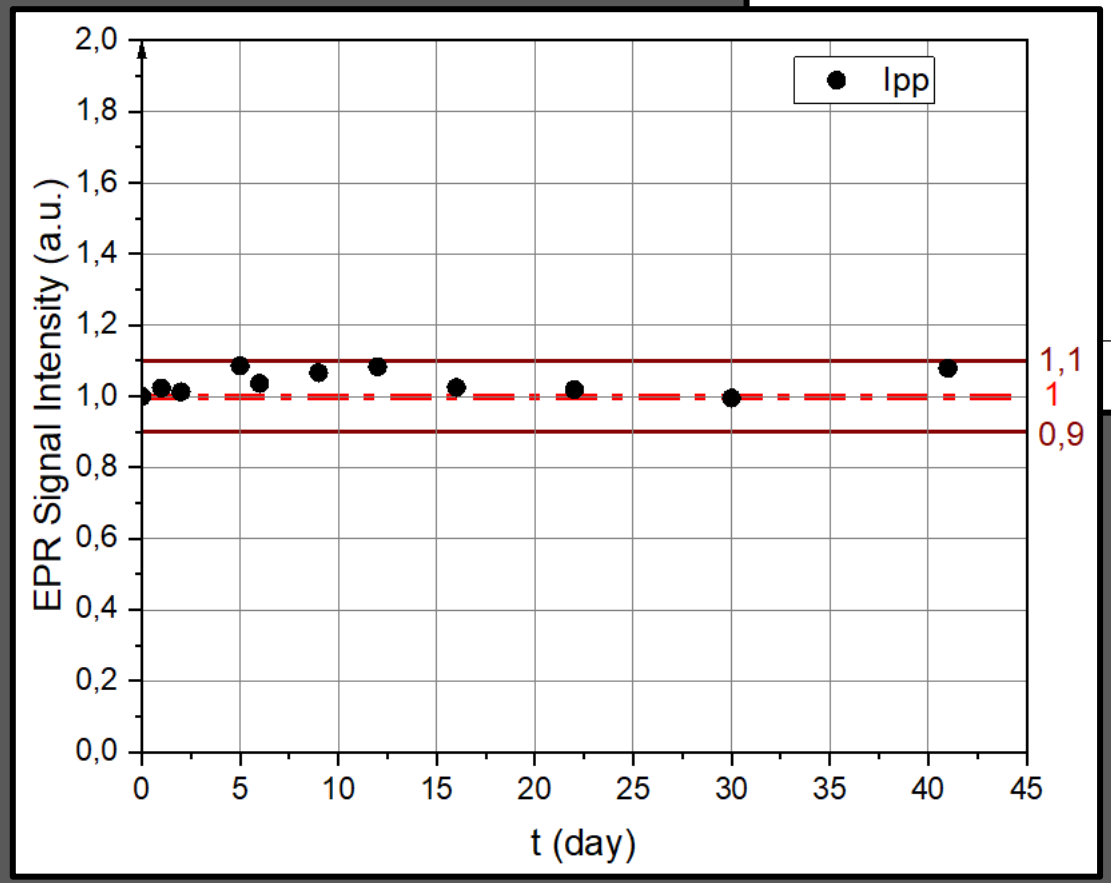
Peak-to-peak signal intensity,

- **not changed at 50 °C**
- **Decreased 10% at 65 °C**
- **Decreased 20% at 80 °C**

It was determined that at least two radicals, highly stable (long-lived) and unstable (short-lived) were formed in the sample with radiation.

Fading Study





Considering the spectra recorded at different dates after irradiation, it is understood that the radical is quite stable.

Results:

- Unirradiated Opagis drug is diamagnetic.
- The drug become paramagnetic after irradiation. EPR signals were observed due to radiation induced radical.
- According to microwave power at both 20 ^{o}C and -150 ^{o}C it was thought that radiation produced more than one radical. Thus, we suggest to take into consider the I_{pp} for dosimetric purposes.
- By considering dose response study, it was observed that EPR signal intensities increased by increasing radiation dose. Thus, the radiation induced radical depends on radiation.
- Linear polynomial function ($y = y_0+ax$) was best fitted to the dose response curve of peak-to-peak EPR signal and the fit parameters were determined.
- According to high temperature and room temperature kinetic studies it was observed that the radiation dependent radical was stable.
- As a result, Opagis drug can be used as an EPR radiation dosimeter between the dose ranges of 10 Gy – 700 Gy.

Thanks for listening

Selcuk University, Konya, TURKEY