Dosimetry of the biological studies on MMW thermal effects in Japan

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Outline

• Exposure setup and Experimental dosimetry.

• Threshold analysis for cornea damage.

• Numerical dosimetry and Mathematical modeling to estimate the threshold of cornea damage.

• Study on over 100GHz.
INTRODUCTION
Searching threshold level of corneal damage exposed to MMW EMF

• Eye ball is sensitive tissue in living body
  – Especially, we have to consider thermal effect due to MMW exposure

• Performing exposure experiment with rabbit eye and numerical analysis to investigate threshold level of power density.
<table>
<thead>
<tr>
<th>Reports of millimeter wave</th>
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<tbody>
<tr>
<td><strong>Frequency</strong></td>
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</table>
| Rosenthal (1977) | 35 GHz 107 GHz CW | • <50 mW  
• 15~80 min (Single exposure)  
• Anesthetize +  
• Eye lids open by tape  
• Circular horn applicator in contact with eye | Rabbit | • 107GHz: immediate corneal stromal damage, it was gone by next day.  
• 35GHz: persistent corneal damage, almost always present the next day. |
| Kues (1999) | 60 GHz CW | • 10 mW/cm²  
• 8 hr (Single Exposure)  
• 4 hr × 5 days  
• Circular horn antenna | Rabbit  & Monkey | Neither microscopic examinations nor the diagnostic procedures performed on the eyes of acute and repeatedly exposed rabbits found any ocular changes that could be attributed to millimeter-wave exposure at 10 mW/cm². |
| Chalfin (2002) | 35 GHz 94 GHz PW | • 0~11J/cm²  
• Anesthetize +  
• 2 W/cm² 35GHz:1.5~5.0s  
94GHz:2.0~4.0s  
• ~8W/cm², 1.0s  
• Open ended waveguide  
• Retained ocular blink reflex | Monkey | The threshold of the cornea injury (epithelial edema, fluorescein staining)  
• 35GHz: 7.5 J/cm²  
94GHz: 5 J/cm²  
Endothelial cell counts remained unchanged. |
EXPOSURE SETUP AND EXPERIMENTAL DOSIMETRY
Example of Exposure system at 95 GHz

• Maximum input power at the lens antenna: approximately 450 mW
  • It comes from insertion loss at waveguides.
• Maximum incident power density: 200 mW/cm²
• Exposure on/off is controlled with switch.

- SG:QBO-9530WSOGE (Quinstar, Input power 1W)
- Switch: QWM-W00000 (Quinstar)
- Directional coupler: QJR-W20300 (Quinstar)
- Power sensor: W8486A (Agilent)
- Power sensor: W8486A (Agilent)
- Power meter: E4419B (Agilent)
- Lens antenna 135 mm
- Rabbit ocular
Standardized exposure system
Temperature measurement for ocular tissue

• Temperature measurement was performed by
  – IR thermography (to measure corneal surface)
  – Fiber optic temperature probe (to measure stroma of cornea and lens)
  – Micro-Encapsulated Thermo-chromic liquid Crystal (to measure aqueous humor)
Temperature development
(30min, 75GHz, 200mW/cm²)

Average of 5 rabbits

Temperature rise in the Surface of cornea is the highest of all at 75GHz.
Estimation of temperature distribution @150mW/cm²

- Upper row: captured images of temperature distribution
- Lower row: 2D temperature distributions estimated from captured image
- Temperature distributions are displayed with very high spatial resolution as 20 x 20 µm
THRESHOLD ANALYSIS FOR CORNEA DAMAGE
Fluorescein staining of damaged cornea epithelial cell

**Former methods**
- S.W. Rosenthal, 1976
- S. Chalfin, 2002

- Rosenthal
- Only the exciter filter
- 2 % Fluorescein, 1 drop
- Surplus fluorescence washing
- Chalfin (No detail)

**KMU methods**
- M. Kojima, et al., 2009

- The exciter filter
- Excitation light cutting filter
- 0.05 % Fluorescein
- 25 µl instillation
- Surplus fluorescence washing
maximum likelihood estimation with generalized linear model (GLE)

- Hereafter, the values of MMW power density which indicate the threshold of eye damage are defined as damaged dose (DD).
- Maximum likelihood estimation (MLE) were performed with probit model for the experimental data to estimate the threshold level for cornea damage.
  - “R” language is used for the MLE.
Cumulative distribution function (CDF) for the probit analysis

\[ p(x) = \int_{-\infty}^{\alpha + \beta x} \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}} \, dz \]

\[ x = \log_e w_{\text{in}} \]

Here \( w_{\text{in}} \) is incident power density.

Coefficients of \( \alpha \) and \( \beta \) are determined by the method of maximum likelihood.
Fitting result for 75GHz, 6min exposure (Corneal Epithelium Damage)
Estimation of damaged dose for corneal epithelium damage

<table>
<thead>
<tr>
<th>Frequency [GHz]</th>
<th>DD10 [mW/cm²]</th>
<th>DD50 [mW/cm²]</th>
<th>DD90 [mW/cm²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>40GHz</td>
<td>50.0</td>
<td>+67.6</td>
<td>+92.0</td>
</tr>
<tr>
<td></td>
<td>-28.7</td>
<td>-60.2</td>
<td>-327</td>
</tr>
<tr>
<td>75GHz</td>
<td>93.1</td>
<td>+41.3</td>
<td>+30.3</td>
</tr>
<tr>
<td></td>
<td>-28.6</td>
<td>-24.6</td>
<td>-47.2</td>
</tr>
<tr>
<td>95GHz</td>
<td>86.2</td>
<td>+45.9</td>
<td>+37.8</td>
</tr>
<tr>
<td></td>
<td>-29.9</td>
<td>-29.9</td>
<td>-70.2</td>
</tr>
</tbody>
</table>

• DD10, DD50, and DD90 is estimated from each result of MLE for 40, 75, and 95GHz exposure.
• “+” and “-” denotes upper and lower limit of 95% confidence interval, respectively.
The dependence of DD on frequency (corneal epithelium damage)
NUMERICAL DOSIMETRY AND MATHEMATICAL MODELING TO ESTIMATE THE THRESHOLD OF CORNEA DAMAGE
Heat transport mechanism

- The temperature elevation is highly localized within several hundred μm depth from the surface of the cornea.

- Heat transport becomes complex in anterior chamber because of the existence of the aqueous humor and such a heating process.

Energy absorption is occurred.

Heating transportation pattern

- Conduction
- Convection
Fine voxel models for rabbit and human

- These models are medically supervised.
- Mesh size is 50µm.
- These models are consists of 7 tissues, cornea, aqueous humor, iris, lens, vitreous humor, sclera, and skin.
Dependence of T and V on the frequency
200mW/cm² 40GHz, 95GHz

t = 360s
Dependence of time constant on the frequency

As for time constant, result by mathematical model is consistent with long time constant obtained by experiment data.
Temperature distribution
40GHz@200mW/cm²

Rabbit

Human

Time: 360 (s)
Temperature distribution 40GHz@200mW/cm²

**Rabbit**

**Human**

Time: 0 (s)
Comparison of temperature change between rabbit and human (40GHz@200mW/cm²)

Human eye is superior in the heat transport ability, because of its deeper anterior chamber depth.
Quantification of thermal dose

• The method to determine the thermal dose has been proposed for cancer therapy from 1984.[1-3]
  – This method is termed “thermal isoeffective dose”
  – Recently this method is considered to apply to estimating threshold caused by thermal effect of MRI equipment.[4]
• The time–temperature data are converted to an equivalent number of minutes at 43ºC
  – 43ºC is the near the break point for CHO and several other cell lines.

CEM43ºC

• Index of thermal isoeffective dose originally defined as follows.

\[ CEM \ 43^\circ C = tR^{(43-T)} \]

  – CEM 43ºC: cumulative number of equivalent minutes at 43ºC
  – t: time interval (min)
  – T: average temperature during time interval t.
  – R: the number of minutes needed to compensate for a 1º temperature change either above or below the breakpoint.

• As for cornea, thermal exposure causes

  – 21 < CEM43ºC < 40 min: Acute and minor damage
  – 41 < CEM43ºC < 22000 min: Acute and significant damage
  – 22000 < CEM43ºC: Severe damage.
CEM43°C distribution at 6min (75GHz 150mW/cm²)

- CEM43°C distribution on the cornea surface.
- Exposure condition is 75GHz, 150mW/cm².
- An example of 6min exposure.

CEM43°C is more than 21 minutes inside the circle

-21< CEM43°C < 40 min: Acute and minor damage
-41< CEM43°C < 22000 min: Acute and significant damage
-22000 < CEM43°C : Severe damage.

Cornea damage is predicted inside the circle by CEM43°C analysis.
Comparison between experiment and mathematical model (CEM43ºC)

Threshold dose level predicted by CEM 43ºC model is fairly agree with the DD50 dose level.
Preliminary investigation for blinking

Blinking effect on the cornea surface temperature is investigated to discuss actual condition.

-75GHz, 50mW/cm²
-Behind the eye lid temperature is assumed 35°C
-Heat transfer coefficient is assumed 20-100 W/Km²

The duration of a blink is 0.1-0.4sec [5]

For the duration of blinking, cornea surface temperature decreases 0.1-0.3 °C in rough estimation

We will conduct more investigation for the effect of eye blinking.

STUDY ON OVER 100GHZ
The concept of high power exposure system with the Gyrotron

Gyrotron FU CW G V @Fukui Univ.

Establishment of the animal breeding facility

0.16THz high power exposure apparatus is being developed with the Gyrotron to observe cornea (eye) damage.

- Preliminary experiment is performed by exposing agar phantoms to the 0.16THz electromagnetic wave.

Tentative animal breeding facility is also being developed at Fukui Univ.

- Adjustment of environment is examined near the Gyrotron facility.
0.16THz exposure example of ager phantom

Peak Power >10W, duty ratio:10%, pulse cycle:1s

- We observed about 100ºC temperature elevation with this condition.
- By using Gyrotron system, we can investigate cornea damage for short time exposure.
Summary

• We have performed experimental and numerical dosimetry for 40, 75, and 95GHz.
  – Temperature elevation of human is smaller than that of rabbit.

• By performing probit model analysis, DD10, DD50, and DD90 are obtained based on in vivo exposure experiment.
  – This analysis is useful to decide the threshold dose.

• Threshold dose level predicted by CEM 43ºC model is fairly agree with the DD50 dose level.

• We will plan over 100GHz (THz) in vivo exposure experiment in future work.
Thank you for kind attention.
MMW Exposure condition

<table>
<thead>
<tr>
<th>Frequency [GHz]</th>
<th>40, 75, 95</th>
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<tbody>
<tr>
<td>Power density [mW/cm²]</td>
<td>200</td>
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- The position of corneal surface is adjusted to the focal point of the lens antenna.
- The incident power density is spatially averaged over a region of φ -13 mm.
  (which is the average size of the rabbit ocular area, and this value is used to determine exposure level.)
The configuration of multi-physics simulation system

The system is consists of 2 part:

**EMF analysis**

- **Method**:
  - 3D scattered-field FDTD (Finite Difference Time Domain) method + rabbit eye model

  induced electromagnetic field in the rabbit eye → SAR

**Heat Transport analysis**

- **Method**:
  - SMAC (Simplified marker and cell) method

  Temperature and flow velocity + (pressure)

- **Heat Transportation**
  - Heat Convection
  - Heat Conduction

- SAR (Specific Absorption Rate)
Equations for heat transport simulation

- Non-compressive fluid
- Boussinesq approximation
- **SMAC (Simplified marker and cell) method** is used

**Physical constants**
- Density: $\rho$ [kg/m$^3$]
- Coefficient of kinematic viscosity: $\nu$
- Specific heat: $C_p$ [J/kg · K]
- Heat conduction coefficient: $K$ [W/m · K]
- Metabolic heat: $A_0$ [W/m$^3$]
- Coefficient of blood flow: $B$ [W/m$^3$ · K]
- Heat source: $Q$ [W/m$^3$]
- Gravity: $g$ [m/s$^2$]

**Continuity equation**

$$\nabla \cdot \vec{V} = 0$$

**Navier-Stokes equation**

$$\frac{\partial \vec{V}}{\partial t} + (\vec{V} \cdot \nabla)\vec{V} = -\frac{1}{\rho} \nabla p + \nu \Delta \vec{V} + \vec{g}$$

**Biological heat transport equation**

$$\rho C_p \left( \frac{\partial T}{\partial t} + (\vec{V} \cdot \nabla)T \right) = \nabla \cdot (K \nabla T) + A_0 - B(T - T_{blood}) + Q$$

**Calculation of pressure**

$$\Delta p = \frac{\rho}{\partial t} \nabla \vec{V}^*$$

**Convective energy transport term**

$$SAR = \frac{\sigma E^2}{\rho}$$

**Variables**
- Velocity: $\vec{V}$ [m/s]
- Temperature: $T$ [°C]
- Pressure: $p$ [kg/m$^2$]
Temperature

**Sclera and skin:** $\Gamma_1$

\[ T = T_{\text{const}} \]

isothermal boundary

**Body temperature:** $T_{\text{const}} = 39^\circ\text{C}$

**Interface with air:** $\Gamma_2$

\[ \vec{q} \cdot \hat{n} = h(T - T_{\text{air}}) \]

Heat transfer coefficient: $h = 20.0 \text{W/(m}^2\cdot{^\circ}\text{C)}$ [3]

**Air temperature:** $T_{\text{air}} = 22 - 24^\circ\text{C}$

Velocity

**Non slip condition on the boundary:** $\Gamma_3$

\[ \vec{V} = 0 \]

Treat pressure as potential. Explicit boundary condition is not given

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Exposure time and Incident power density of the threshold

\[ y = A \cdot \exp(-B \cdot x) + y_0 \]

- \( A = 76851 \pm 3.83 \times 10^4 \)
- \( B = -0.036918 \pm 0.00383 \)
- \( y_0 = 56.447 \pm 14 \)

95% confidence interval
Estimation of time constant from mathematical model

- Time constant is estimated from threshold diagram of time and power density.
- Time constant is 270 s and 170 s for 40 GHz and 75 GHz exposure, respectively.
- The values of time constant become small as the frequency increase.
CEM43°C for MMW exposure

• MMW exposure causes temperature elevation in the ocular tissue as a functions of space and time.

• The history of thermal exposure is required to obtain CEM43°C index.

• We modified the definition of CEM43°C as follows

\[
CEM\ 43°C(\vec{r}, t) = \int_0^t R(43°C, t') dt' \text{[min]}
\]

\(T(\vec{r}, t)\): Temperature of ocular tissue obtained by computer simulation

\(t\): Exposure duration

\(R\): \(R=0.25\) at \(T<43°C\), \(R=0.5\) at \(T>43°C\)
For preliminary experiment the Gyrotron is operated at 840mW average power under the pulse mode.
- Peak power: 1.2W, Duty ratio: 70%, Cycle: 1Hz

We got a temperature difference ($\Delta T$) between before and during exposure.
$\Delta T=16^\circ C$ ($34^\circ C$-$18^\circ C$)

This $\Delta T=16^\circ C$ is agree on $\Delta T$ before and during 95 GHz, 300mW/cm$^2$, 6 min ocular exposure.