ELECTRIC POWER RESEARCH INSTITUTE

Results from EPRI Review of Low Dose Health Effects

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Drivers for EPRI study

- BEIR VII report published (draft available in 2005)
  - Inconsistent conclusions reached between BEIR VII report and French Academy report
  - Unable to adequately incorporate results from emergent science in review process
    - Review ended ~2003/2004 but results from several significant studies funded by DOE Low Dose Program were published after that.
- Increasing pressure to implement costly technology with no clear health benefit
- EPRI recognized the need for a more balanced report encompassing latest scientific findings

EPRI Research 2007-2009

- Evaluated published literature that was not included in earlier reports
  - special emphasis on new information published since these reports were issued
- Determine if and how this new literature may impact our understanding of the health effects of low doses of radiation.
- Reviewed >200 publications as part of this evaluation effort.
- Publish summary report addressing the state-of-science and noting gaps and research needs.
- Final document published 11/09 (Product ID: 1019227)

How will the results of this study be used?

- Update our understanding of the science of low dose health effects so that we can align radiation protection practices with radiological risks

- Provide technical feedback and support of NRC regulatory change (10 CFR Part 20 Update)

EPRI Low Dose Research Team

- Project Manager:
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- Principal Investigators:
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  - Dr. Gabor Mezei
  - Dr. Christopher Wood

Key Conclusions from Study (Biological Mechanism Review)

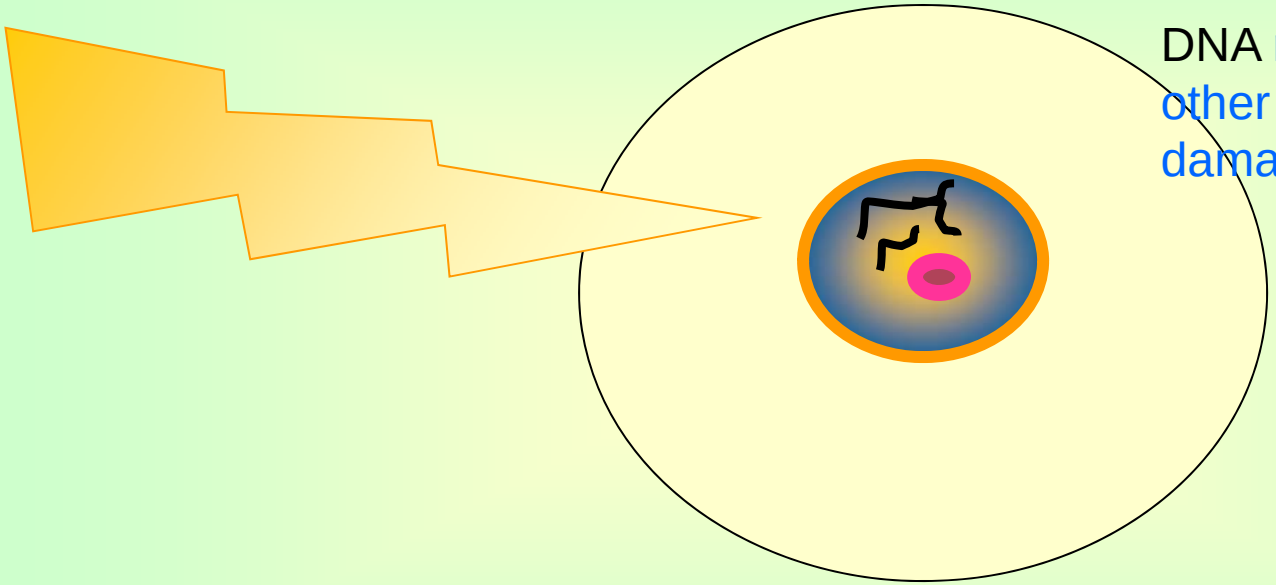
1. Studies in the low dose area demonstrate that the mechanism of action for many biological responses in this area are different than seen in higher dose or higher dose-rate regions.

   – There is a need for expanding the radiation damage/response paradigm to account for increased complexity in biological response mechanisms

Paradigm Shift Needed in Risk Models
(Expansion of Existing Paradigm)

Energy deposited in the nucleus OR cytoplasm

GENETIC SENSITIVITY



DNA may be broken, or other molecules may be damaged

Triggers biological processes:

- Adaptive response
- Bystander effects
- Genomic instability

Biological Mechanisms

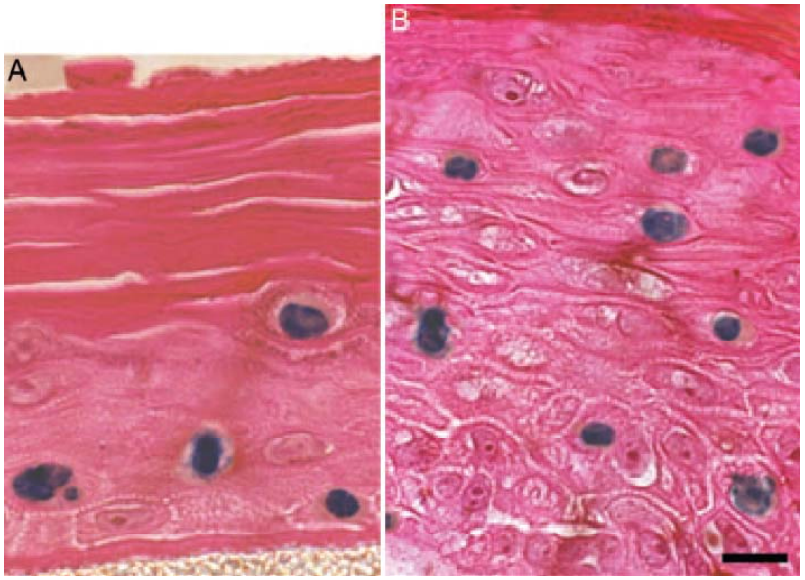
- Adaptive Response
  - Normal Physiologic Response To Mild Stress
    - Induction of DNA Repair Mechanisms
      - Early Exposure To Low Dose May Protect Against Chromosomal Damage From A Subsequent High Radiation Dose
    - Reduction Of Genomic Instability Through Elimination Of Mutated Cells
    - “Hormesis Model”
      - Modification Of Biological Defense Mechanisms At Low Doses

Biological Mechanisms (continued)

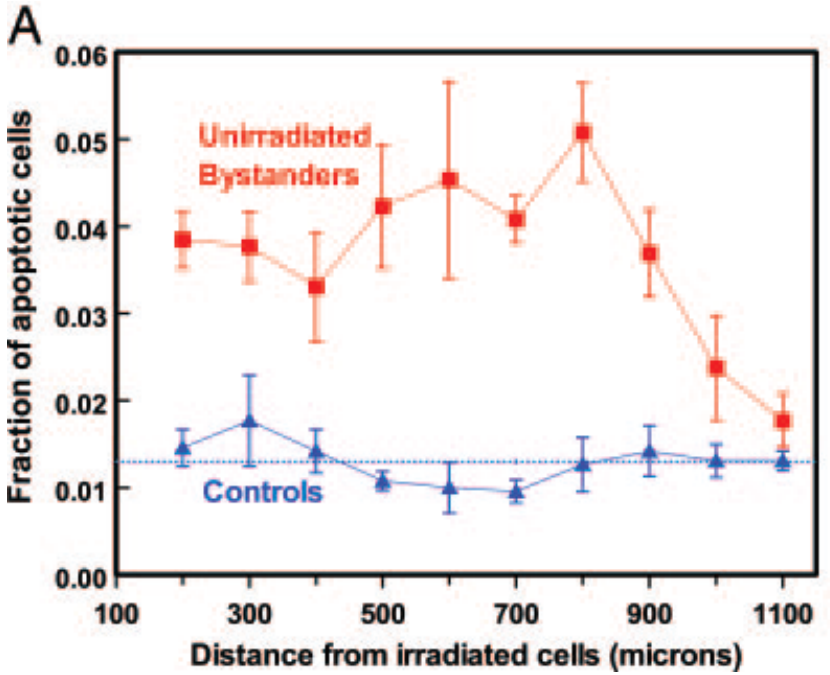
- Bystander Effects
  - Communication From Irradiated Cell To Non-irradiated Cells Resulting in Induction of Biological Responses
  - Mediated Through Secretion Of Chemical Factors Or Transfer Of Molecules Through Gap Junctions
  - Elicits Effects on Non-irradiated Cells
- Genomic Instability
  - Delay Reproductive Death
  - Induce Mutations
  - Effects Triggered In Part By:
    - Bystander Effects
    - Sustained ROS Production

Induction of Apoptosis in Bystander Cells*- Potentially Protective Effect

Elimination Of Damaged Cells Through Apoptosis Could Be Associated With Protective Consequences



Apoptosis in unirradiated, bystander cells >200 μm away in Tissue "A" and Tissue "B"

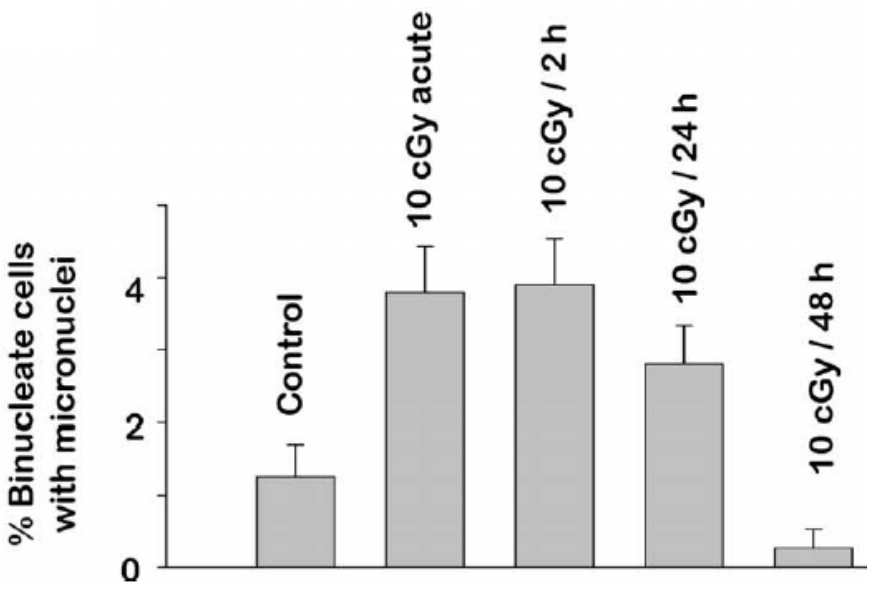


Statistically Significant Bystander Response Seen Up To 1 mm Away From Irradiated Cells

*Belyakov, O.V. et al., 2005. Biological Effects in Unirradiated Human Tissue Induced by Radiation Damage Up to 1 mm Away. Proc National Academy of Sciences. 102(40), 14203-14208.

Next Steps

- Risks due to low dose rate effects may be overestimated; therefore, there is a need to re-evaluate the dose and dose-rate effectiveness factor (DDREF). (Polaris Proposal)
- Influence of dose-rate on DNA damage:



10 cGy = 1 Rad

Reference: Toledo et al*

- Novel 3D tissue culture system→ mimics *in vivo* growth
- Dose-rate matters!
- Level of DNA damage differs depending on dose-rate

***S.M. Toledo, N. Asaad, P. Venkatachalam, L. Li, R. W. Howell, D.R. Spitz, and E.I. Azzam, " Adaptive responses to low-dose/ low-dose-rate gamma rays in normal human fibroblasts: the role of growth architecture and oxidative metabolism," Radiat Res. 166(6), pp.849-57 (2006).**

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