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# **A Review of Depleted Uranium Biological Effects:** ***In vitro* studies**

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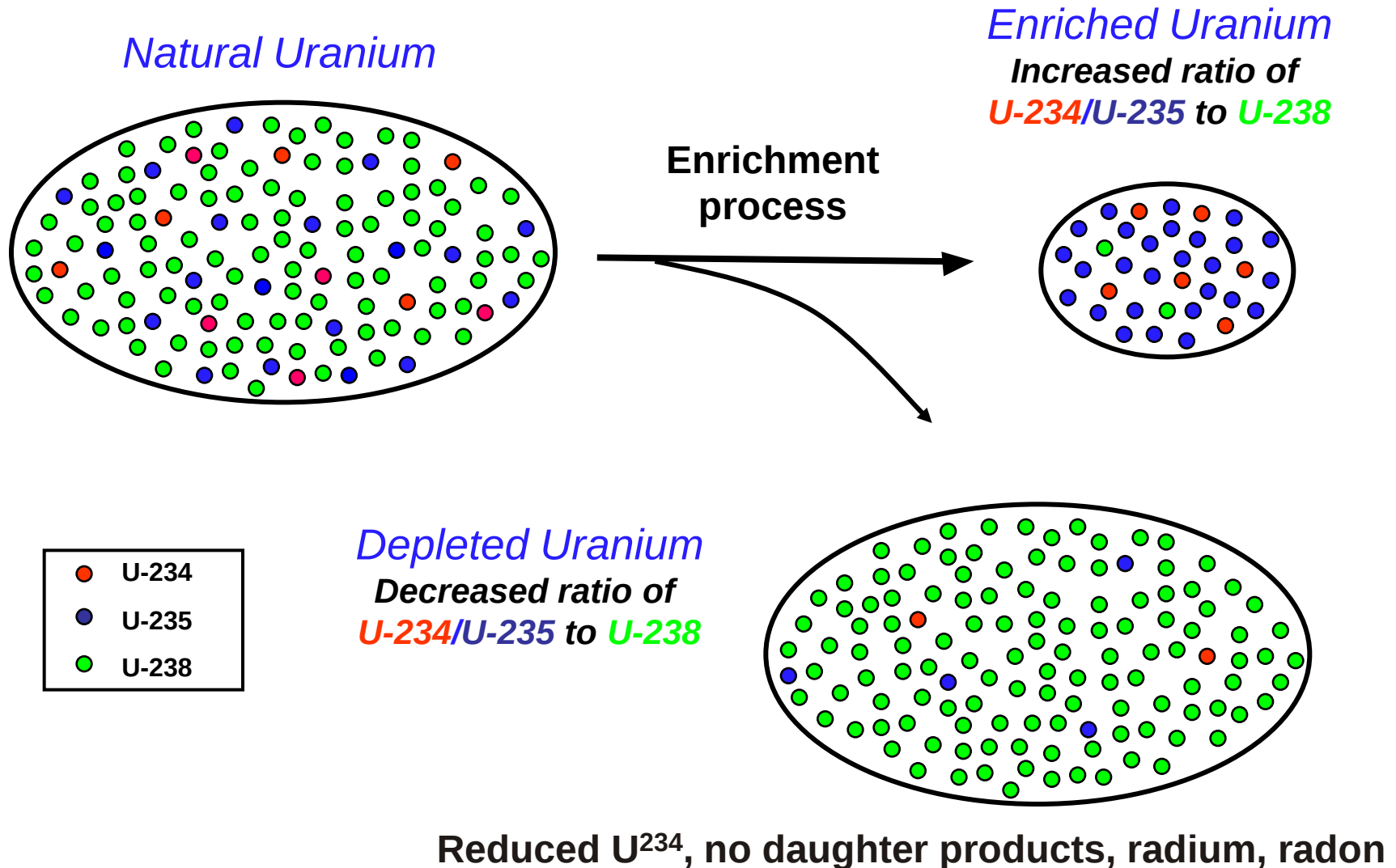
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**Uniformed Services University**  
Armed Forces Radiobiology Research Institute

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| Report Documentation Page                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    |                                     |                                                           | Form Approved<br>OMB No. 0704-0188                  |                                 |
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| 14. ABSTRACT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    |                                     |                                                           |                                                     |                                 |
| 15. SUBJECT TERMS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |                                     |                                                           |                                                     |                                 |
| 16. SECURITY CLASSIFICATION OF:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    |                                     | 17. LIMITATION OF ABSTRACT<br><b>Same as Report (SAR)</b> | 18. NUMBER OF PAGES<br><b>60</b>                    | 19a. NAME OF RESPONSIBLE PERSON |
| a. REPORT<br><b>unclassified</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | b. ABSTRACT<br><b>unclassified</b> | c. THIS PAGE<br><b>unclassified</b> |                                                           |                                                     |                                 |

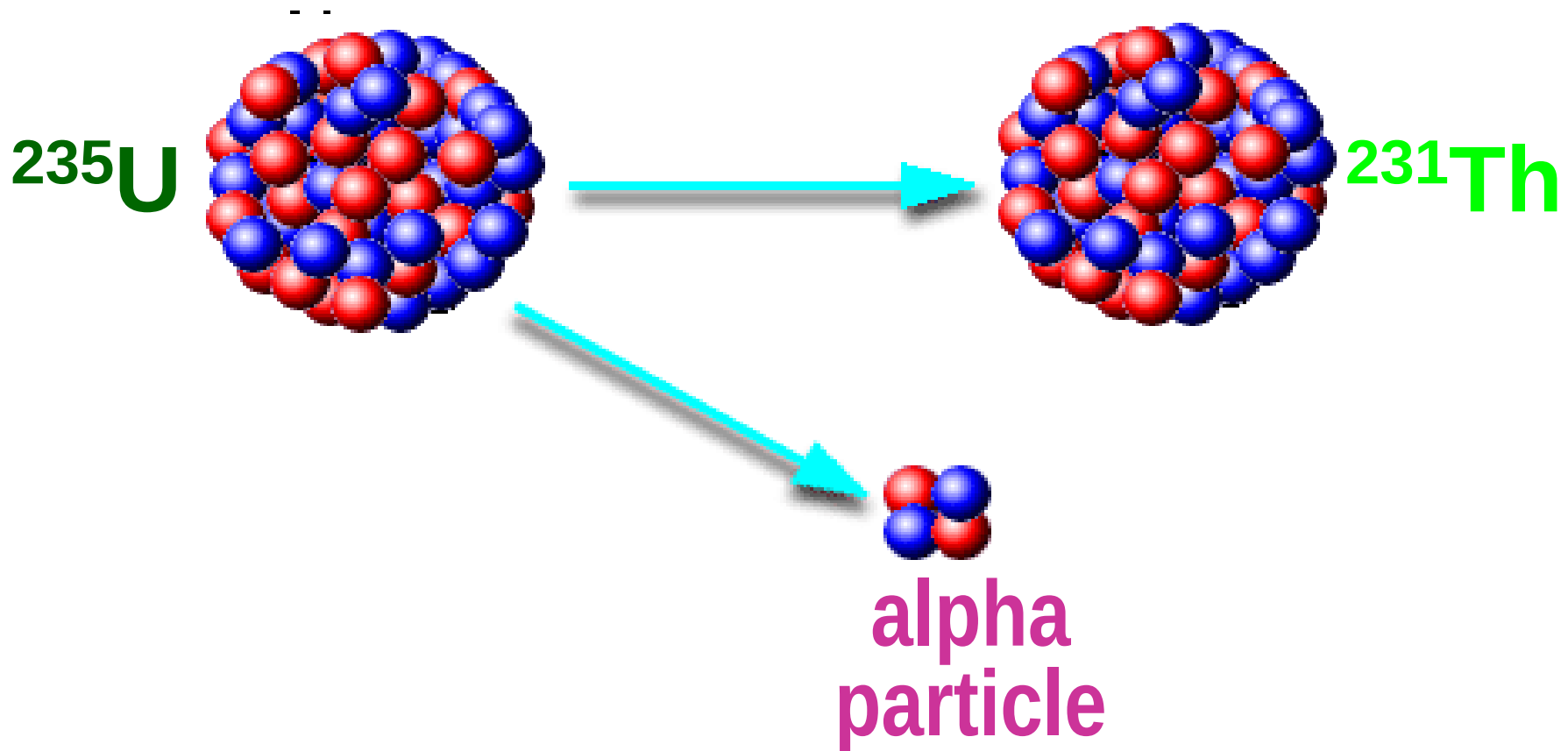
# What is “Depleted Uranium”



# DU is Radioactive:

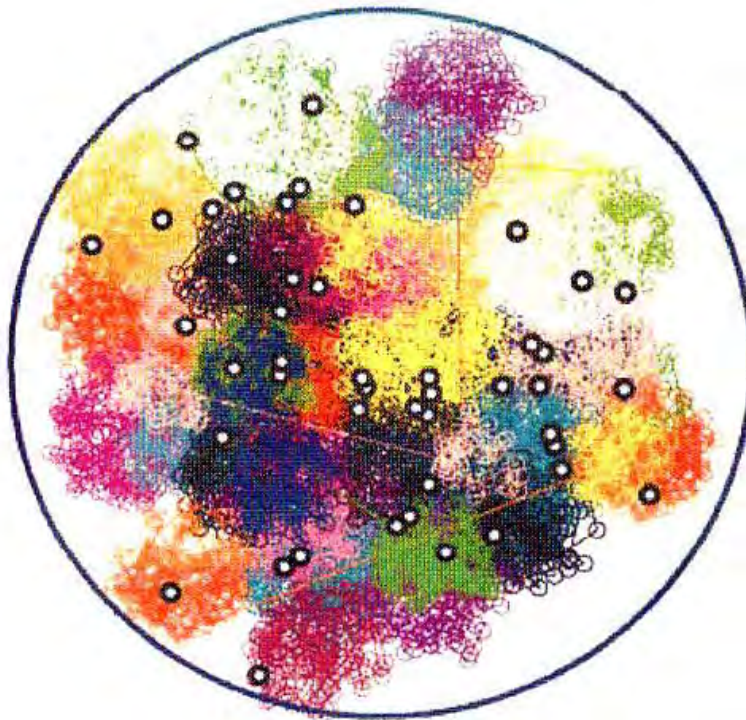
## Alpha Particle Emitter

Spontaneous emission of particles from  
unstable nuclei



Alpha particles are more hazardous than x rays or gamma rays, because they deposit their energy over very small distances

X rays



Alpha particles



o = chromosome break

# Comparison of the Relative Contribution of Uranium Isotopes\* (natural and depleted)

| Isotope                                    | Specific Activity<br>( $\mu\text{Ci/g}$ ) | DU<br>SA by WT%<br>( $\mu\text{Ci/g}$ ) | Natural Uranium<br>SA by WT%<br>( $\mu\text{Ci/g}$ ) |
|--------------------------------------------|-------------------------------------------|-----------------------------------------|------------------------------------------------------|
| $^{238}\text{U}$                           | 0.333                                     | 0.332                                   | 0.331                                                |
| $^{236}\text{U}$ (not naturally occurring) | 63.6                                      | 0.0001                                  | 0                                                    |
| $^{235}\text{U}$                           | 2.2                                       | 0.0044                                  | 0.051                                                |
| $^{234}\text{U}$                           | 6200                                      | 0.093                                   | 0.310                                                |
| <b>Total</b>                               |                                           | <b>0.4295</b>                           | <b>0.692</b>                                         |

\*Contribution of the daughter products is not included.

# **Questions Regarding DU And Its Health and Biological Effects that Prompted Our Research**

- 1) Is long-term exposure to internalized DU carcinogenic?**
- 2) Does DU cause radiation effects?**
- 3) Does DU cause transgenerational effects?**
- 4) Can we distinguish between DU and other exposures (radiation, chemical)?**

# **Research Approach: Follow Regulatory Agency Approach**

**IARC, NTP, FDA, EPA**

## **Carcinogenic Hazard Evaluation**



**Transformation + Mutagenicity + Cytogenicity**



**Animal Carcinogenesis Model**



**Human Epidemiology**

# **Limitations of Using DU Compounds**

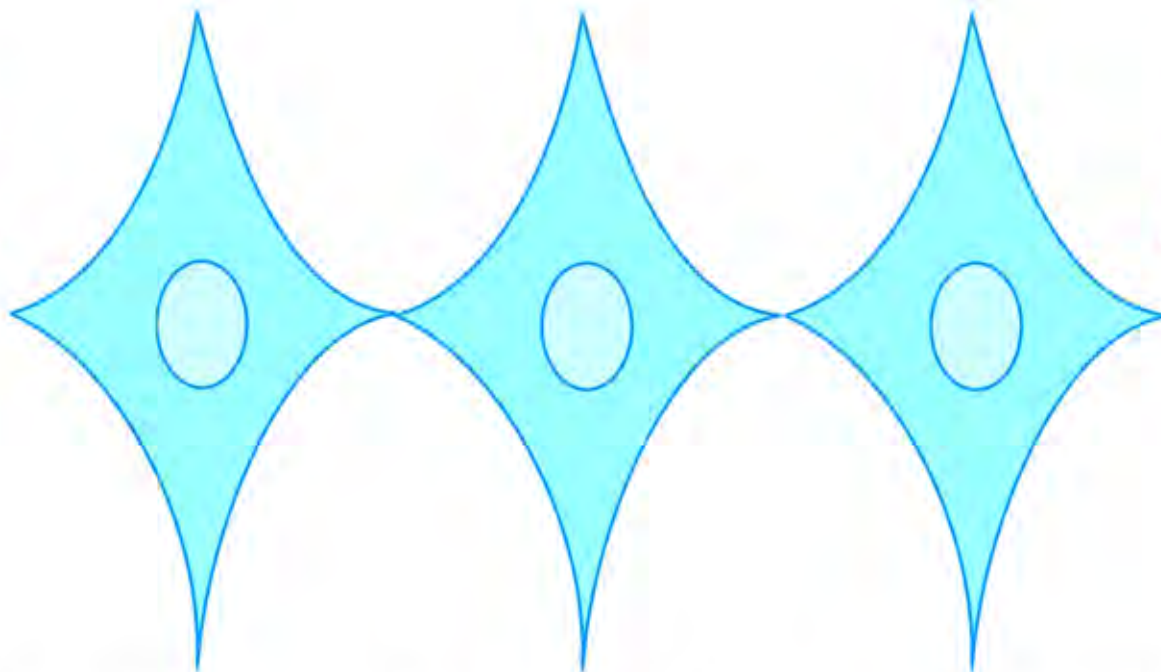
## *in vitro*

- 1) DU- uranyl nitrate, uranyl chloride, acetate (soluble)**
- 2) DU- uranium dioxide (insoluble)**
- 3) Uptake of uranium by cells**
- 4) Radiation dose to cells**

# Radiation Dose Measurement

## "Microdosimetry"

**Alpha  
Particle**



**Alpha  
Particle**



$\leq$  1% cells hit;  
approximately  
18 cGy  
(soluble DU)

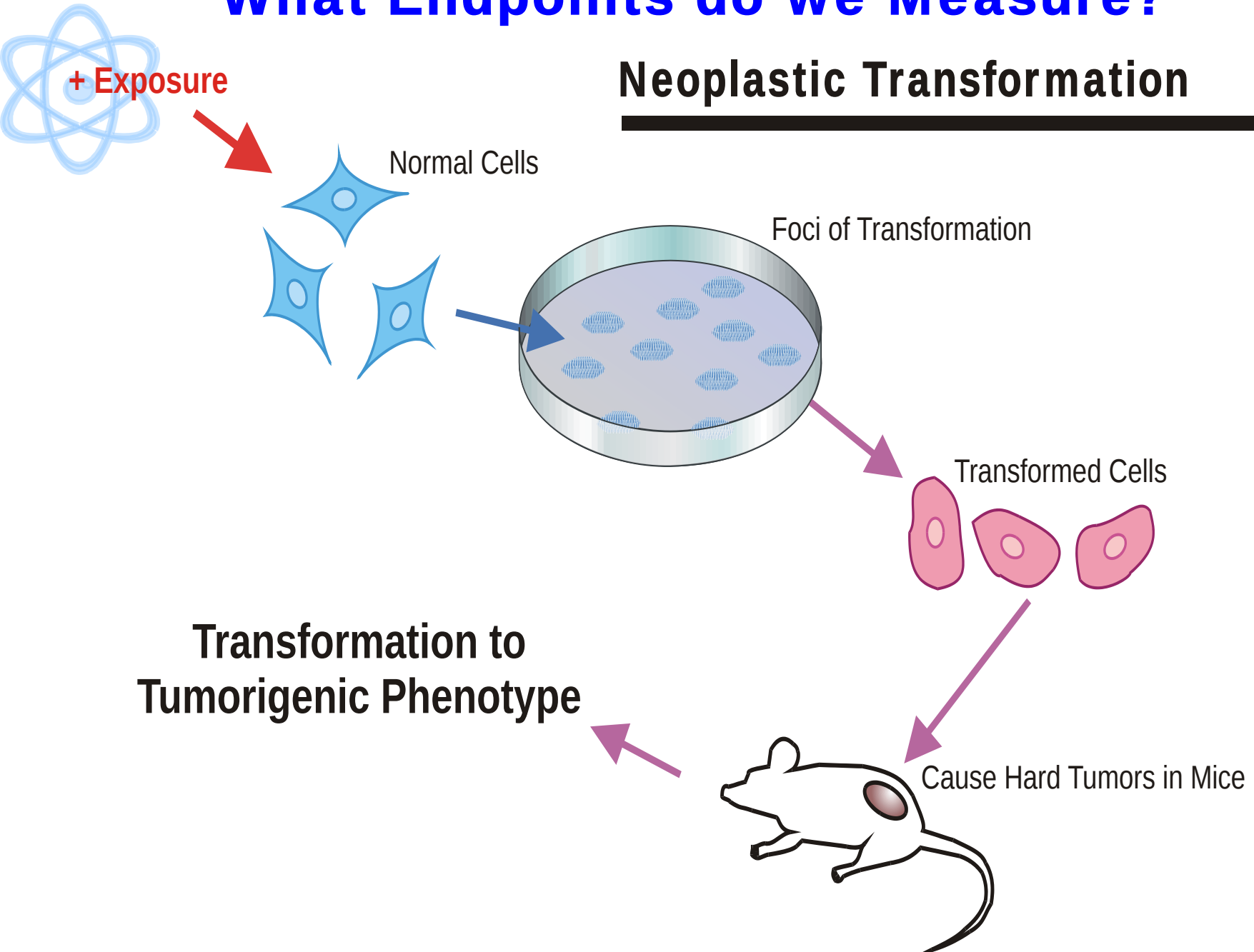
$\leq$  7% cells hit;  
approximately  
22 cGy  
(insoluble DU)

$\leq$  21% cells hit;  
approximately  
24 cGy  
(insoluble DU)

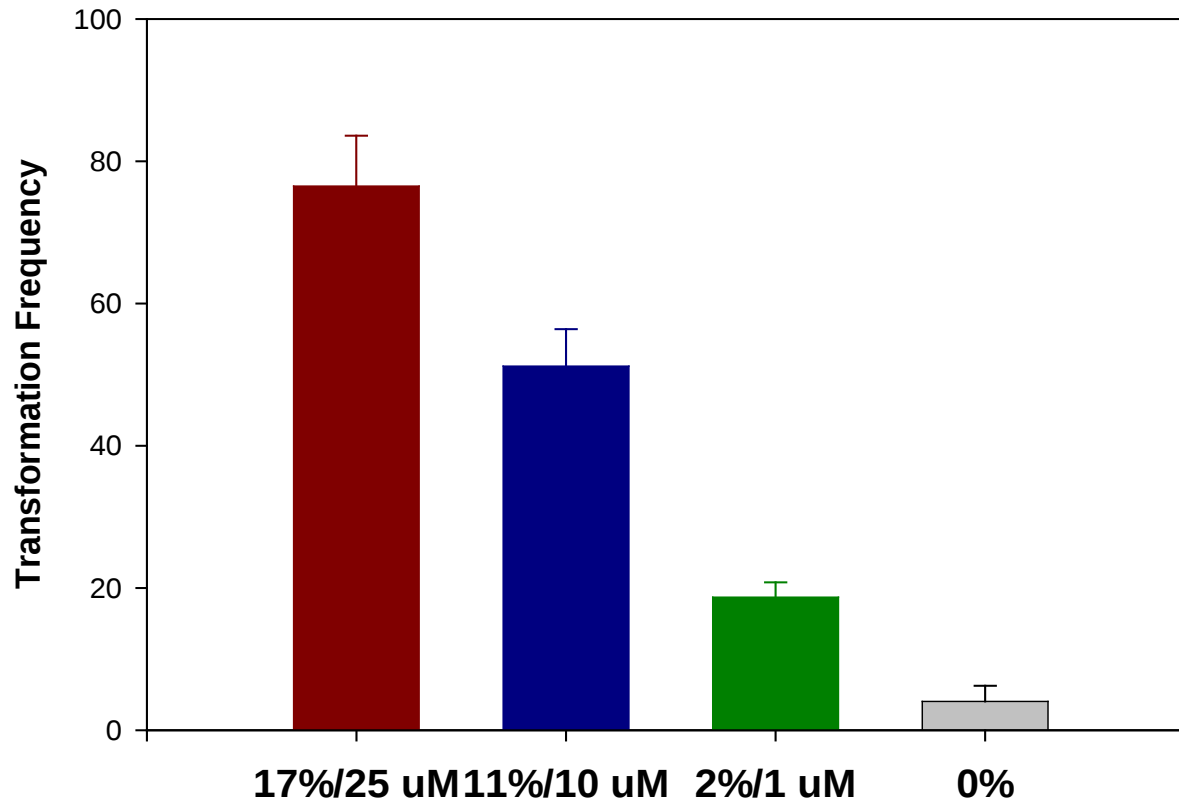
# What Endpoints do we Measure?

## Neoplastic Transformation

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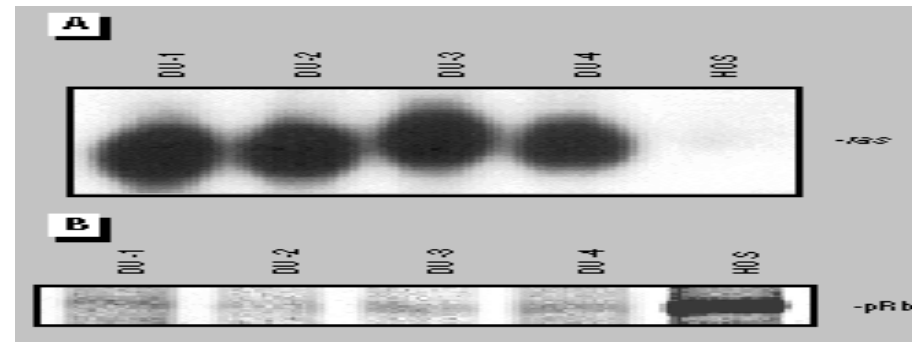
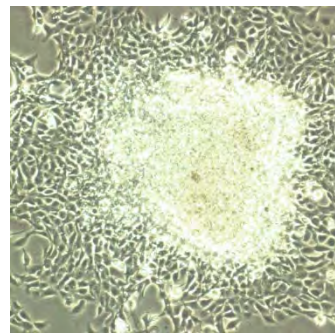
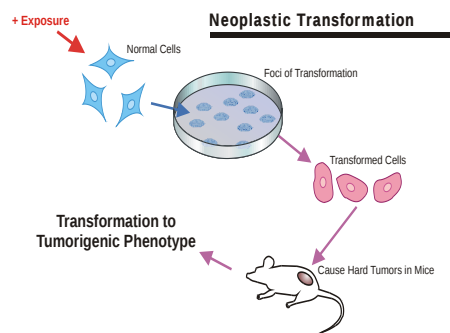
# Comparison of Traversals of Nucleus by Alpha Particles and DU Concentration



# Heavy-Metal Induced Transformation of Human Osteoblast Cells

|                                                                   | Untreated | Ta<br>(soluble) | DU<br>(soluble)<br>(1%) | DU<br>(insoluble)<br>(7%) | DU<br>(insoluble)<br>(21%) | HMTA<br>(insoluble) | Ni<br>(insoluble) | PbCr (IV)<br>(Insoluble) | Alpha<br>Particles<br>5 cGy, 120 keV<br>(100%) |
|-------------------------------------------------------------------|-----------|-----------------|-------------------------|---------------------------|----------------------------|---------------------|-------------------|--------------------------|------------------------------------------------|
| Transformation<br>Frequency<br>(per survivor x 10 <sup>-4</sup> ) | 4.4 ± 1.1 | 5.2 ± 1.0       | 49.6 ± 4.8              | 81.2 ± 6.1                | 269.5 ± 33                 | 37.6 ± 5.1          | 46.5 ± 4.9        | 38.2 ± 4.0               | 68.2 ± 4.0                                     |
| Morphology                                                        | Flat      | Flat            | Transformed             | Transformed               | Transformed                | Transformed         | Transformed       | Transformed              | Transformed                                    |
| Saturation<br>Density<br>(x 10 <sup>5</sup> cells)                | 2.6       | 2.2             | 6.9                     | 6.6                       | 7.1                        | 6.1                 | 7.3               | 5.9                      | 5.9                                            |
| Soft-agar<br>colony<br>Formation<br>(PE%)                         | 2         | 2               | 47                      | 61                        | 78                         | 52                  | 49                | 37                       | 37                                             |
| Tumorigenicity<br>(Mice w/tumors<br>Per Mice w/o)                 | 0/240     | 0/12            | 22/47                   | 33/50                     | 15/20                      | 8/20                | 5/12              | 4/12                     | 4/12                                           |

Miller, et al, *Environmental Health Perspectives*, Vol. 1998; Miller, et al, *Carcinogenesis*, Vol. 22, 2001.

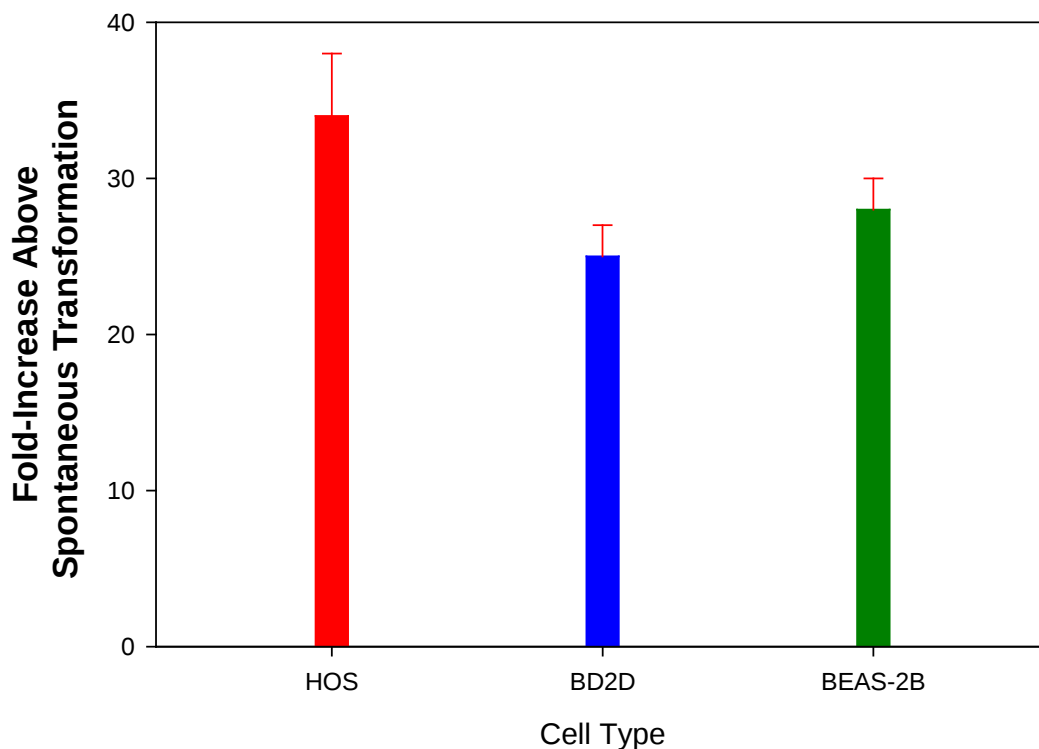


# **Neoplastic Transformation Studies (Multiple Laboratories)**

- 1) Human osteoblast cells (bone) – HOS**  
(Miller et al 1998; Miller et al 2001, Miller et al, 2003; Miller et al 2005)
- 2) Human bronchial cells (lung) – BEP2D** (Xie et al, 2010)
- 3) Human bronchial cells -BEAS2B** (Yang et al, 2010)

# Malignant Transformation by Insoluble DU Compounds

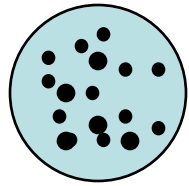
- 1) Human osteoblast cells (bone) – HOS (Miller et al 1998; Miller et al 2001, Miller et al, 2003; Miller et al 2005)
- 2) Human bronchial cells (lung) – BEP2D (Xie et al, 2010)
- 3) Human bronchial cells - BEAS2B (Yang et al, 2010)



# **Mutagenesis Studies**

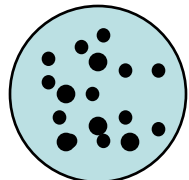
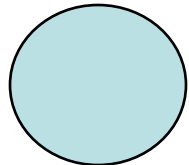
# HPRT Gene ASSAY

## The Hypoxanthine Phosphoribsyltransferase Assay.



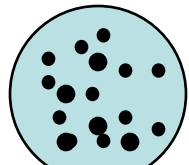
HPRT +/+

6-thioguanine = Poison



HPRT -/-

6-thioguanine = OK



Miller 16

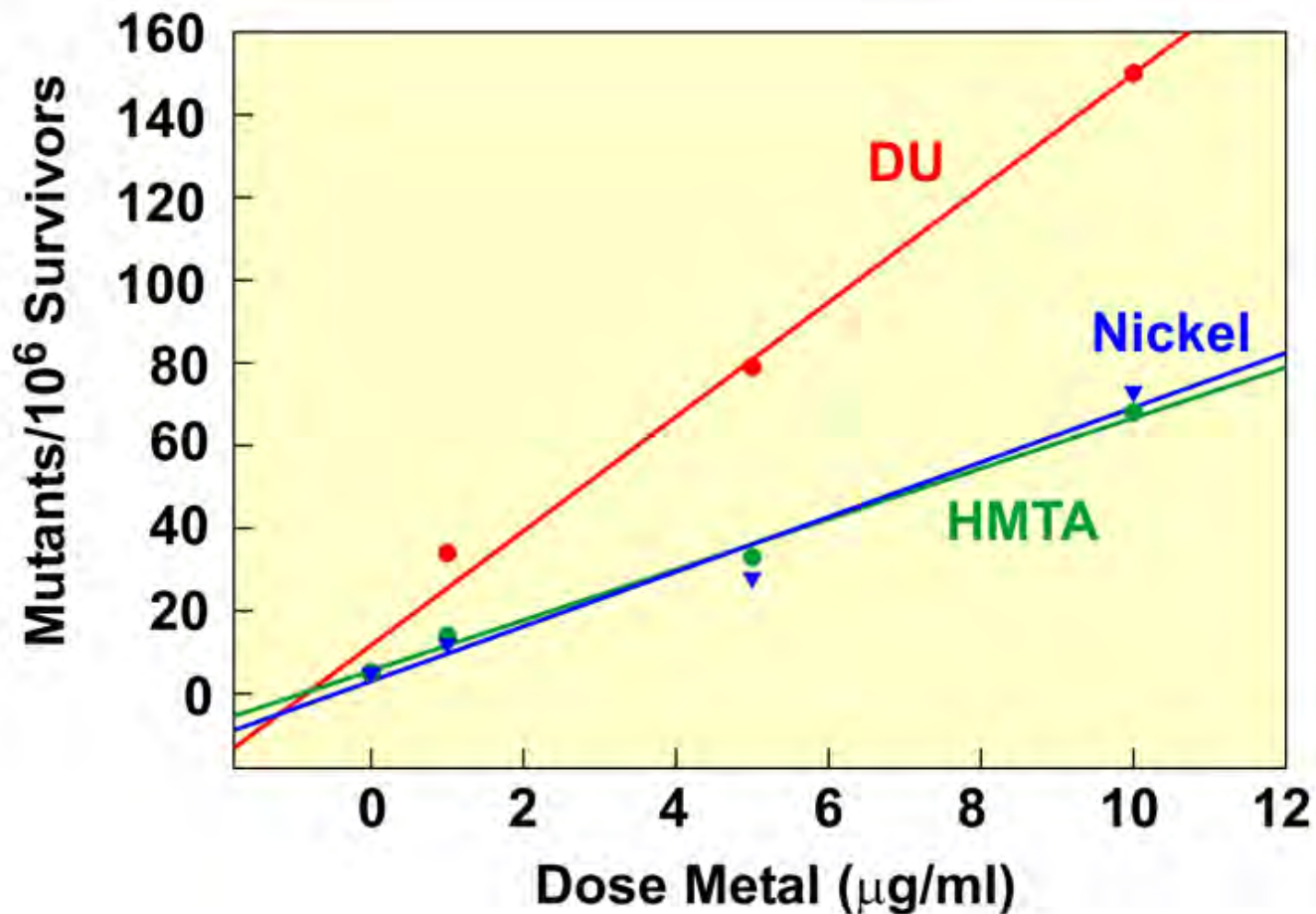
So, if cell acquire mutation in HPRT, it **become resistant** to 6-thioguanine compound



We can **directly count mutant colonies** and compare this number with number of cell seeded on plate

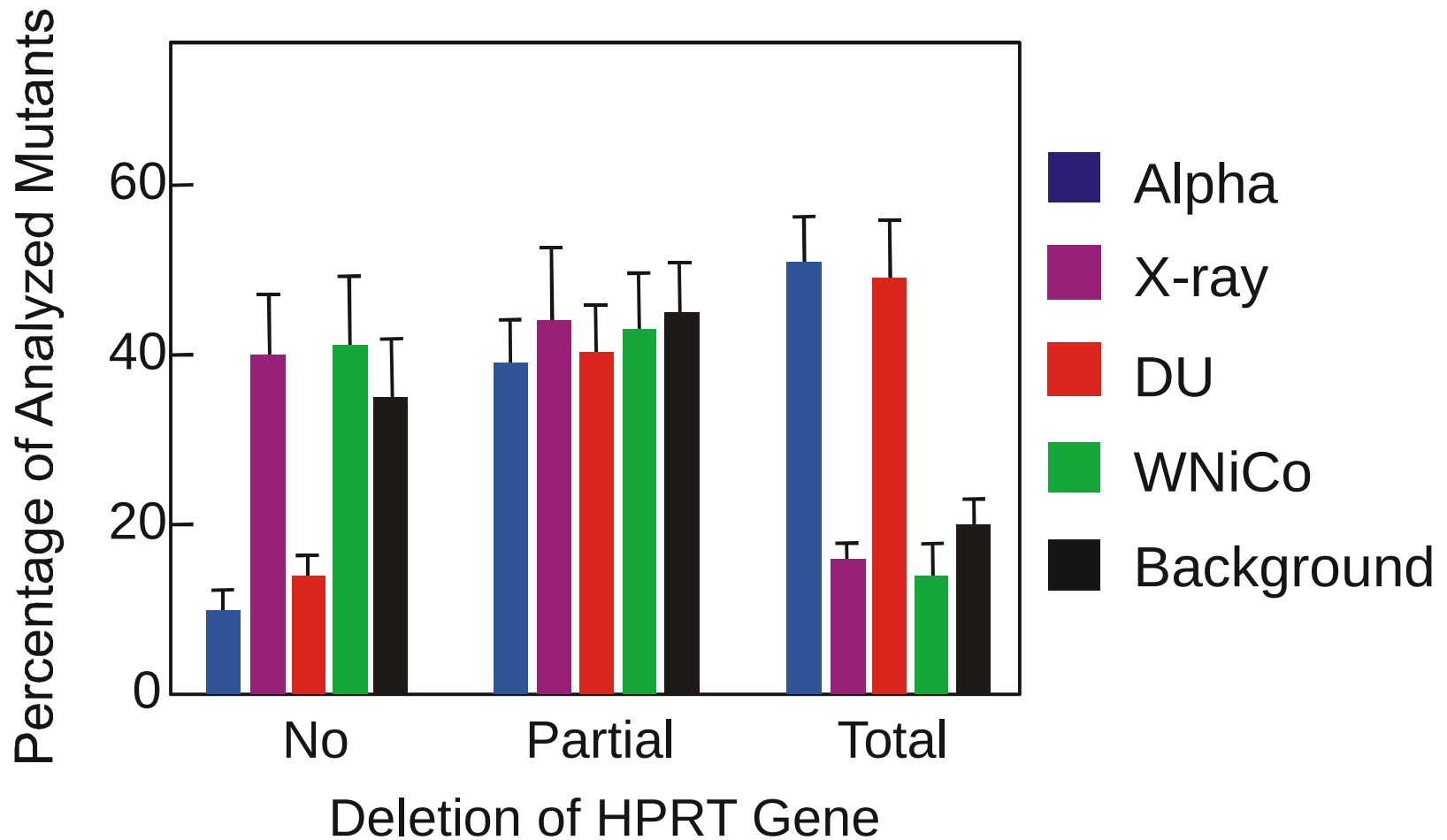
# DU – Uranium Dioxide Mutagenicity

## HPRT Mutations in V79 Cells



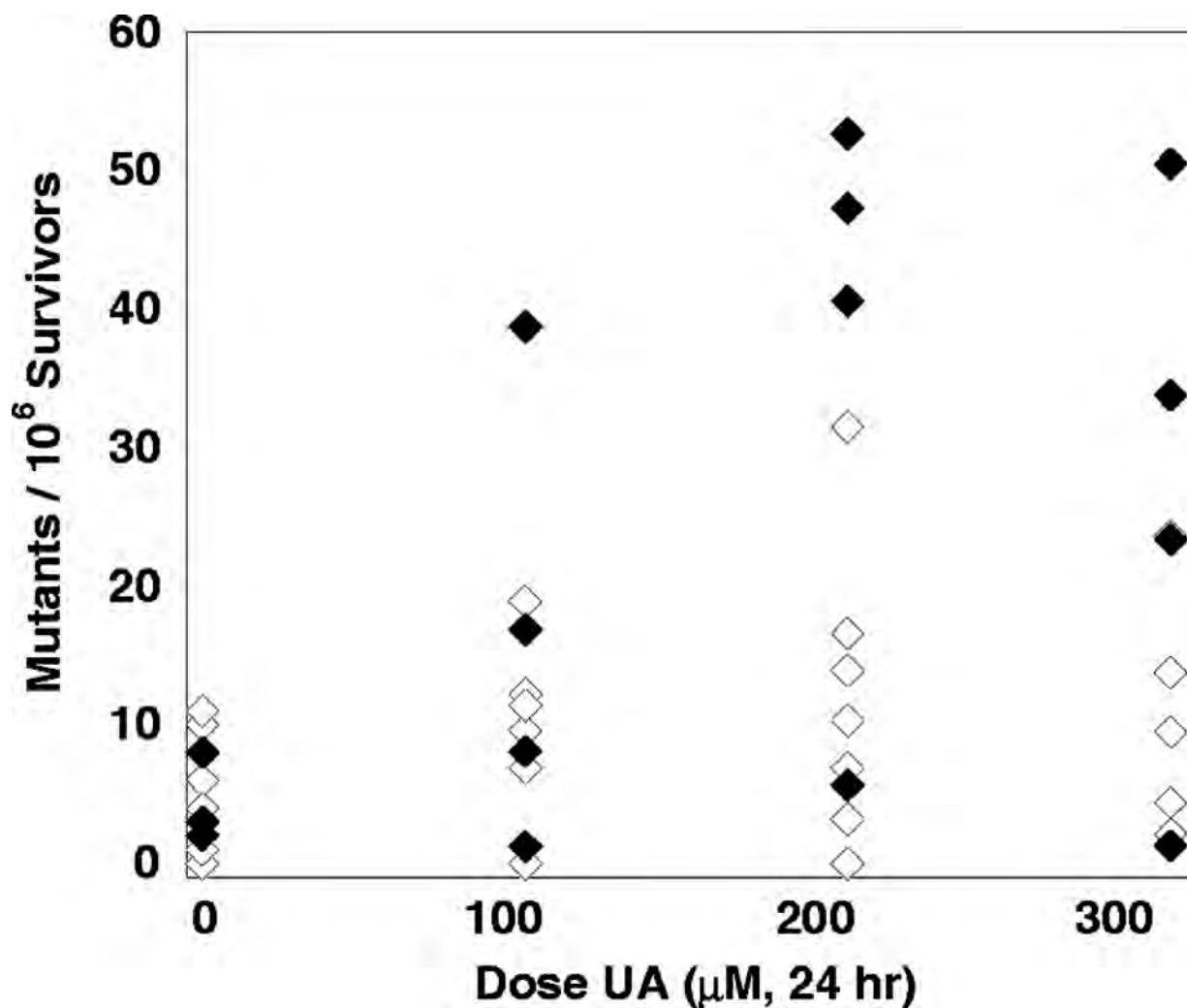
Unpublished data

# Mutation Spectrum of HPRT Gene In V79 Cells



# Mutagenicity of DU-Uranyl Acetate – Stearns Laboratory NAU

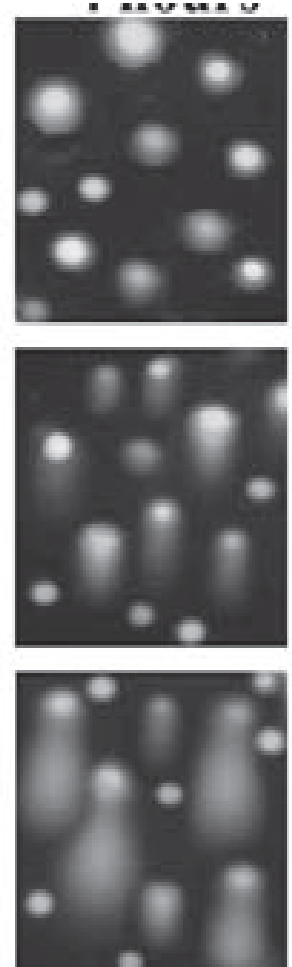
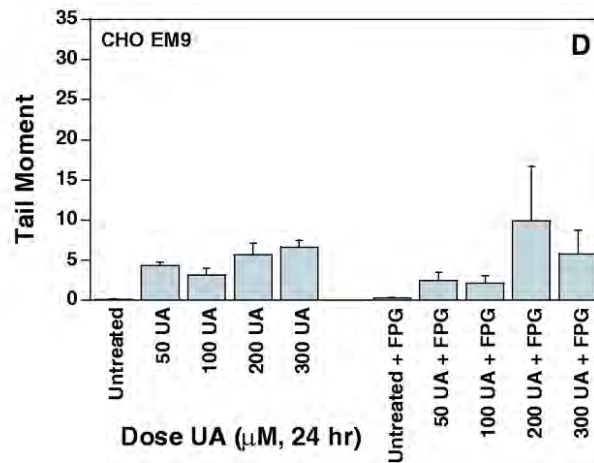
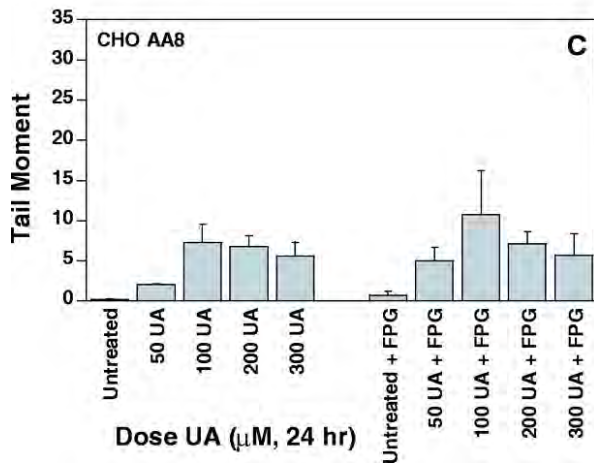
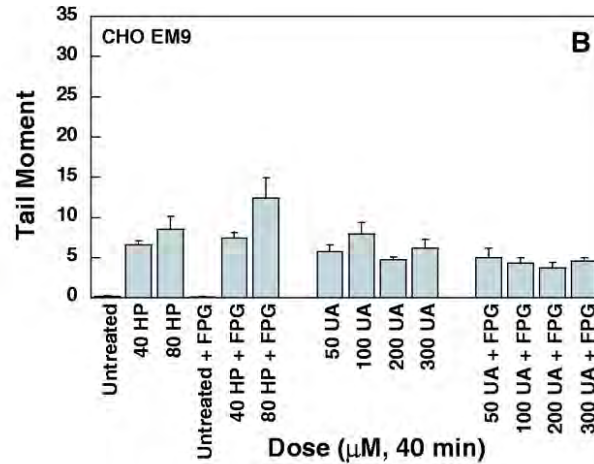
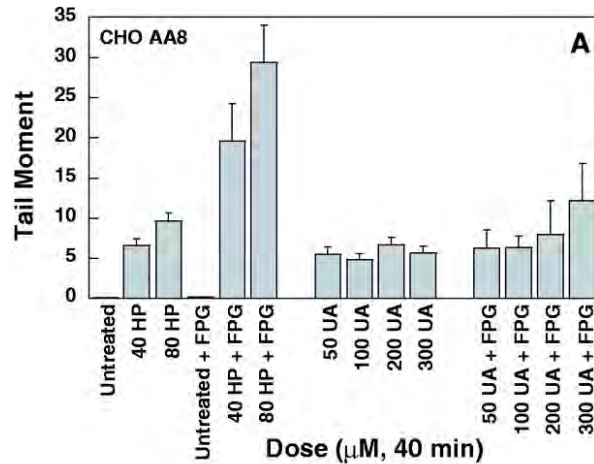
6-Thioguanine-resistant cells obtained after 24 h exposure of CHO-AA8 (open diamonds) and CHO-EM9 (closed diamonds) cells to UA.



# **DNA Damage Studies**

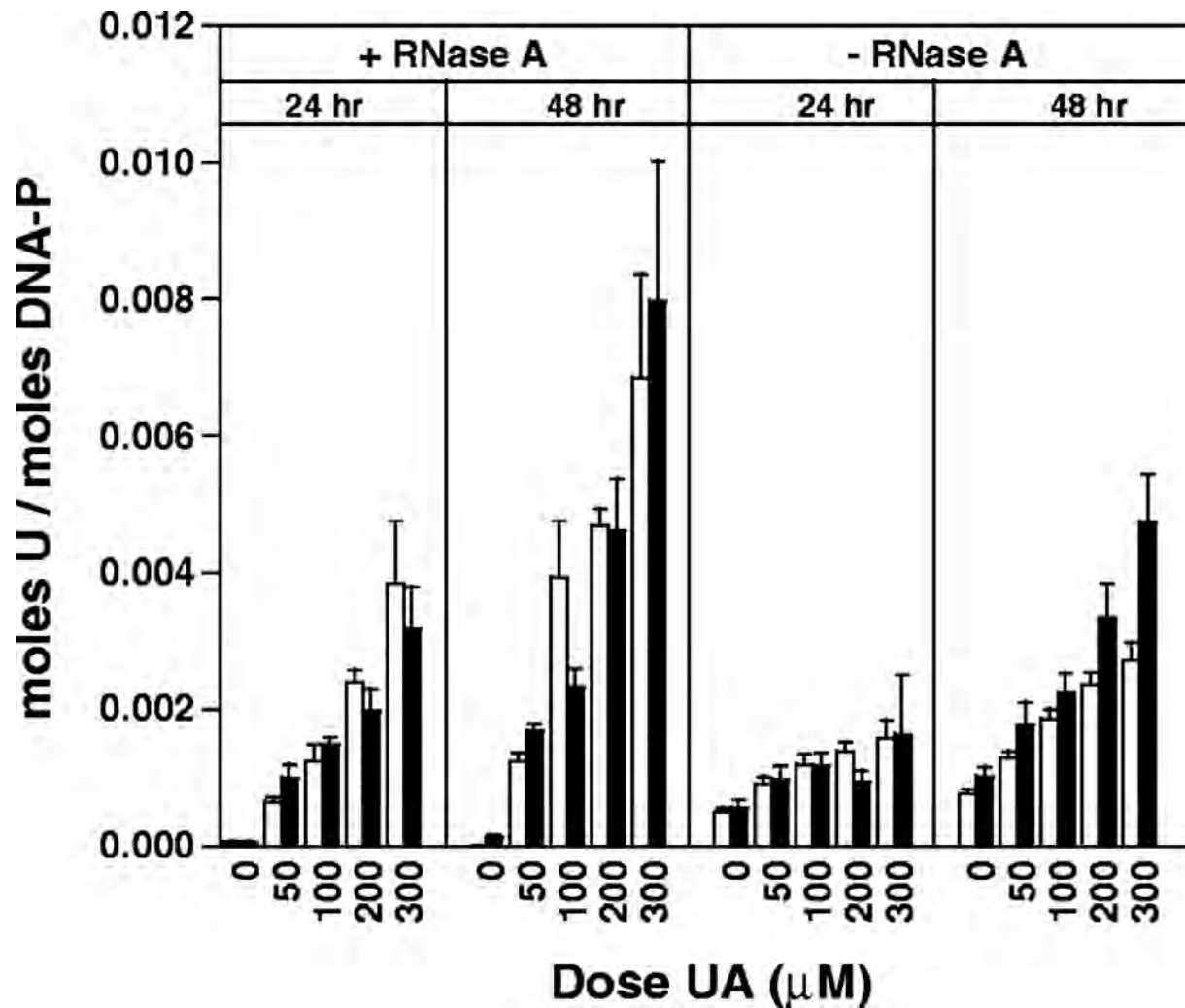
# DNA Damage Induced by DU – Stearns Laboratory NAU

Analysis of DNA damage induced by UA and H<sub>2</sub>O<sub>2</sub> by the comet assay.



# DU Binds to DNA

Measurement of uranium–DNA binding in CHO AA8 (open bars) versus CHO EM9 (closed bars) cells exposed to UA for 24 or 48 h by ICP-OES.



# Genotoxicity Studies

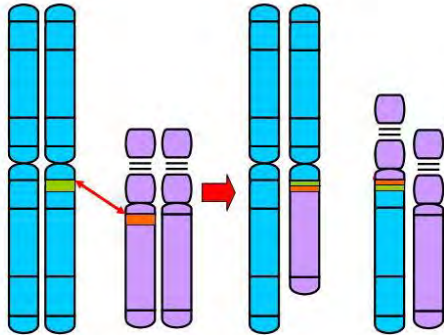
## **Earliest studies with DU in vitro:**

Lin et al, *Mutation research* 1993, Cytogenetic toxicity of uranyl nitrate in Chinese hamster ovary cells.

## **Results:**

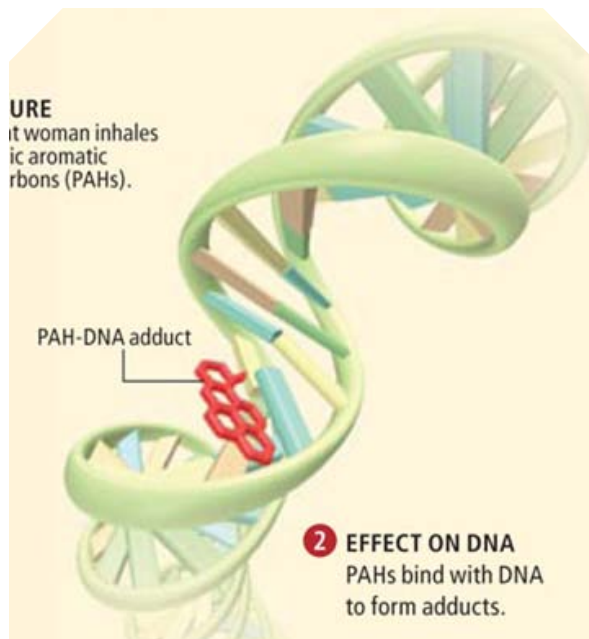
DU induced sister chromatid exchanges (SCEs)

# Chromosomal Changes

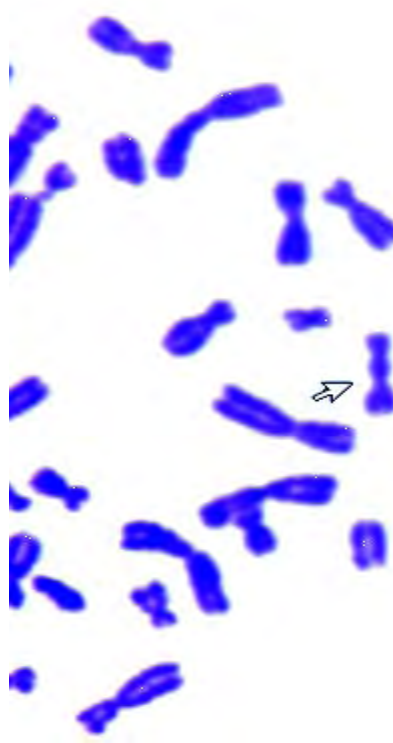


Translocations

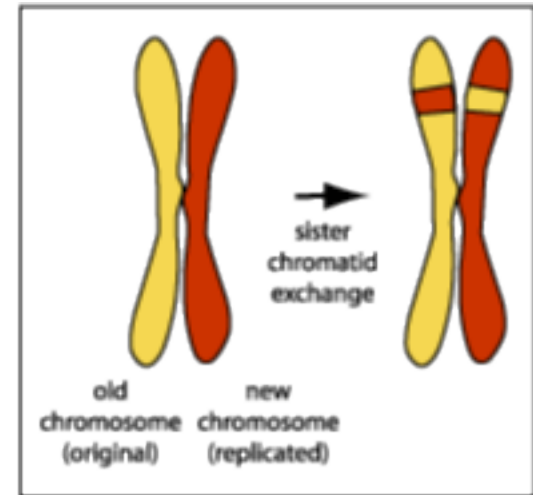
DNA Adducts



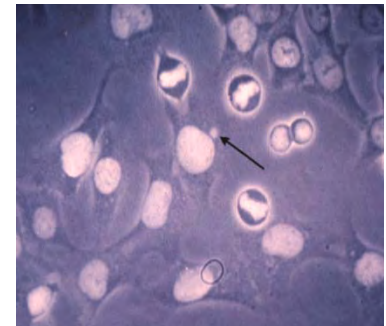
Dicentrics



Sister Chromatid Exchange



Micronuclei



# Short-term Assays: DNA or Chromosome Endpoints

**Mutagenicity:**

**Gene Mutation**

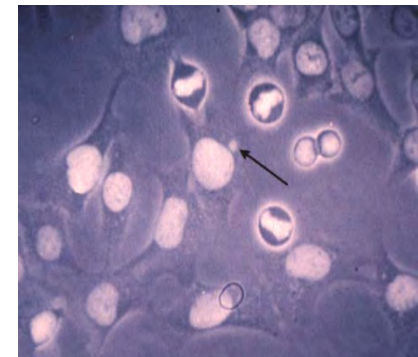
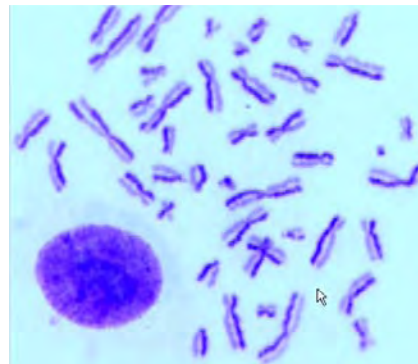
**Cytogenicity:**

**Chromosomal Damage**

**Genomic Instability:**

**Chromosomal damage  
(clonal descendants)**

**HPRT Gene**



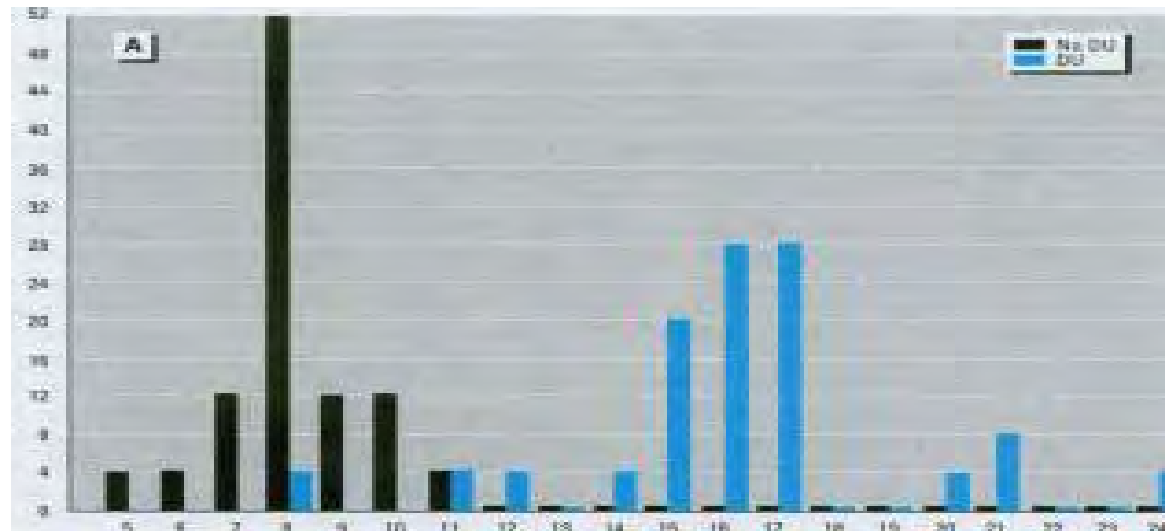
# Heavy Metal Genotoxicity

|                                          | DU<br>(Soluble) | DU<br>(Insoluble) | rWNiCo       | Be | Ni           |
|------------------------------------------|-----------------|-------------------|--------------|----|--------------|
| Micronuclei<br>Induction                 | ↑               | ↑                 | ↑            | ↑  | ↑            |
| Sister Chromatid<br>Exchange             | ↑               | ↑                 | ↑            | ↑  | ↑            |
| DNA Filter Elution<br>(DNA strand break) | ↑               | ↑                 | ↑            | ↑  | ↑            |
| Dicentric Formation                      | ↑               | ↑                 | no<br>change | ND | no<br>change |

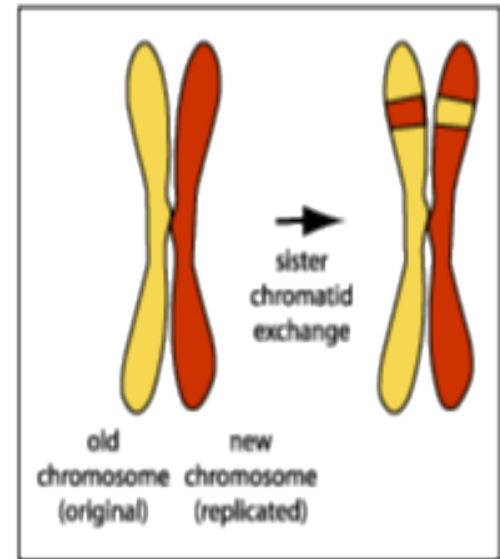
Miller *et al*, *Carcinogenesis*, Vol 22, 2001. Miller *et al.*, *Metal Ions in Biology and Medicine*, Vol 6, 2001.

# Induction of Chromosomal Damage

Frequency of Cells with SCE (%)

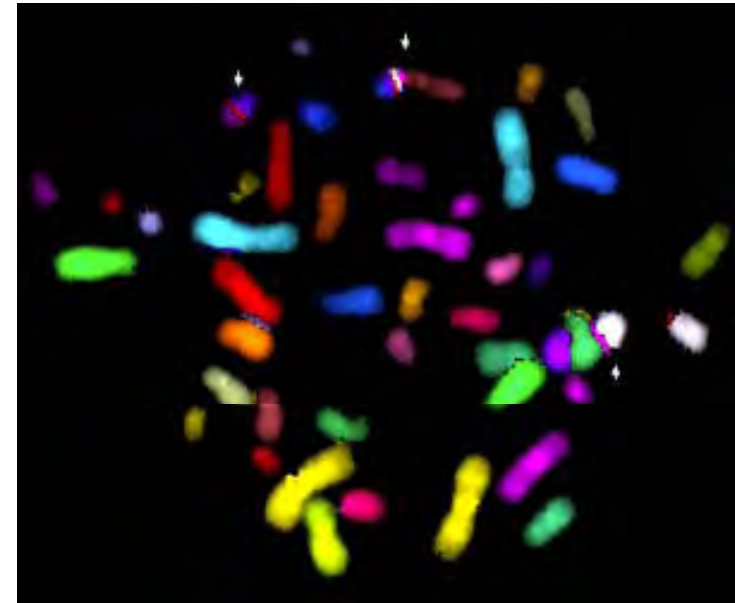
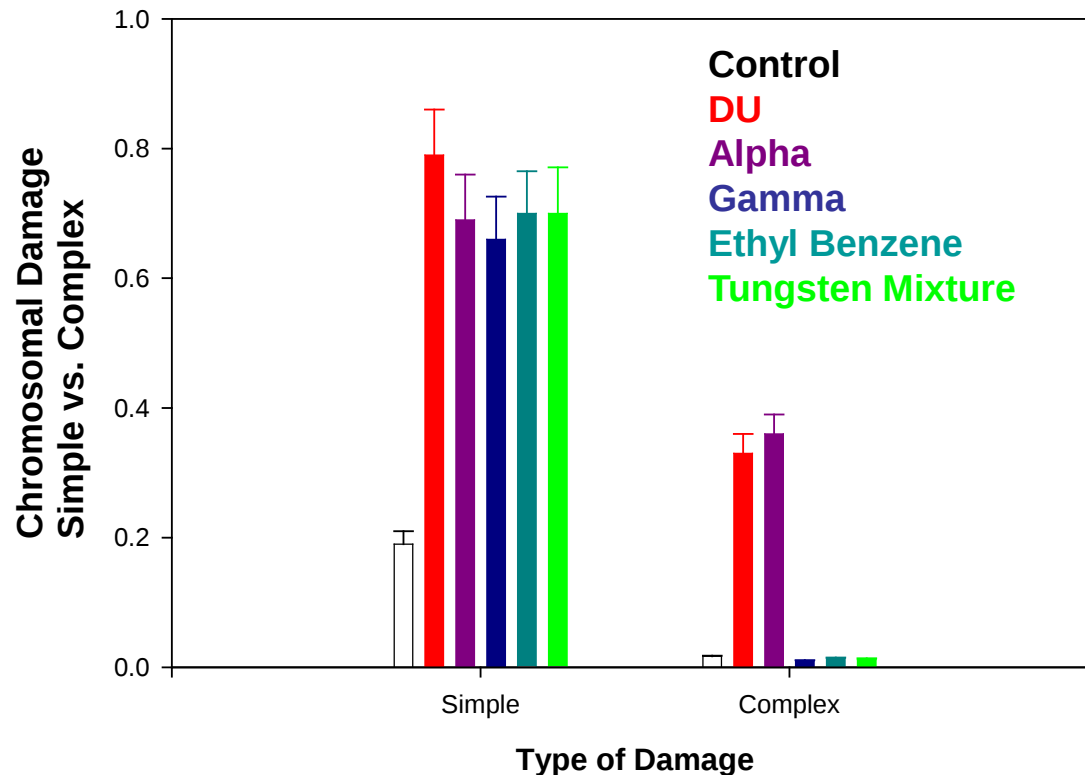


Number of SCE's Per Cell



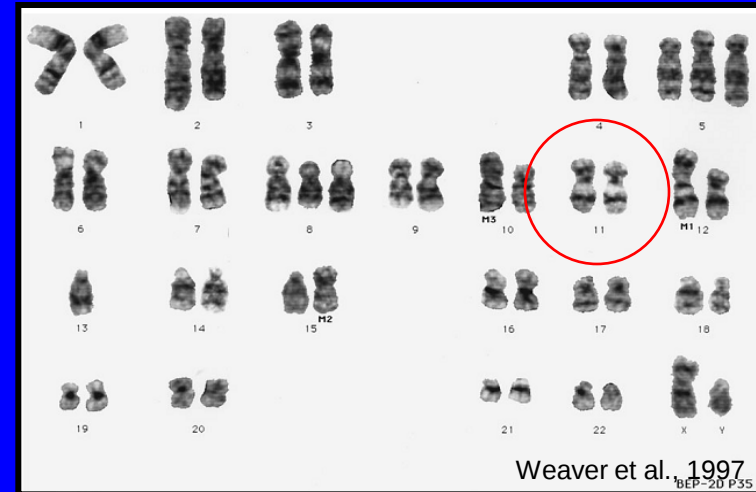
Mechanisms:  
inhibition of DNA replication  
direct damage of chromosomes

# Chromosomal Damage in Human Osteoblast Cells Exposed to DU, Alpha Particles, Gamma Radiation, Tungsten Mixture, Ethyl Benzene *in vitro*

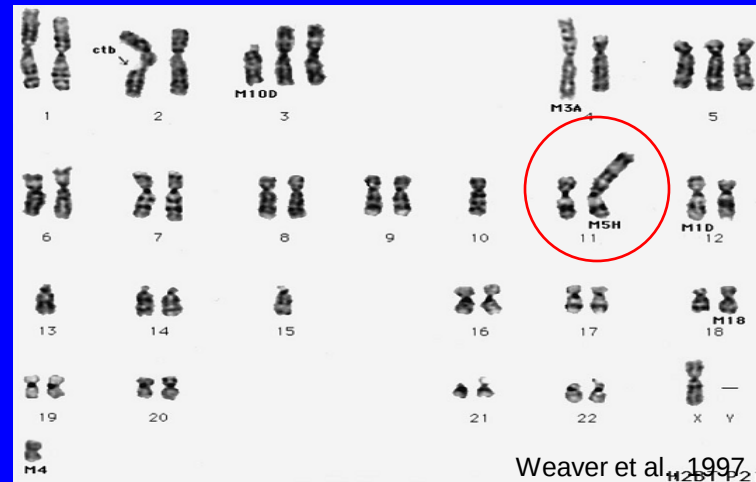


# Chromosome Instability (CIN)

- Hallmark of lung cancer
- Proposed as an early event in carcinogenesis
- 70-80% of lung tumors exhibit CIN
- Complex phenotypes
  - Structural abnormalities
  - Numerical abnormalities



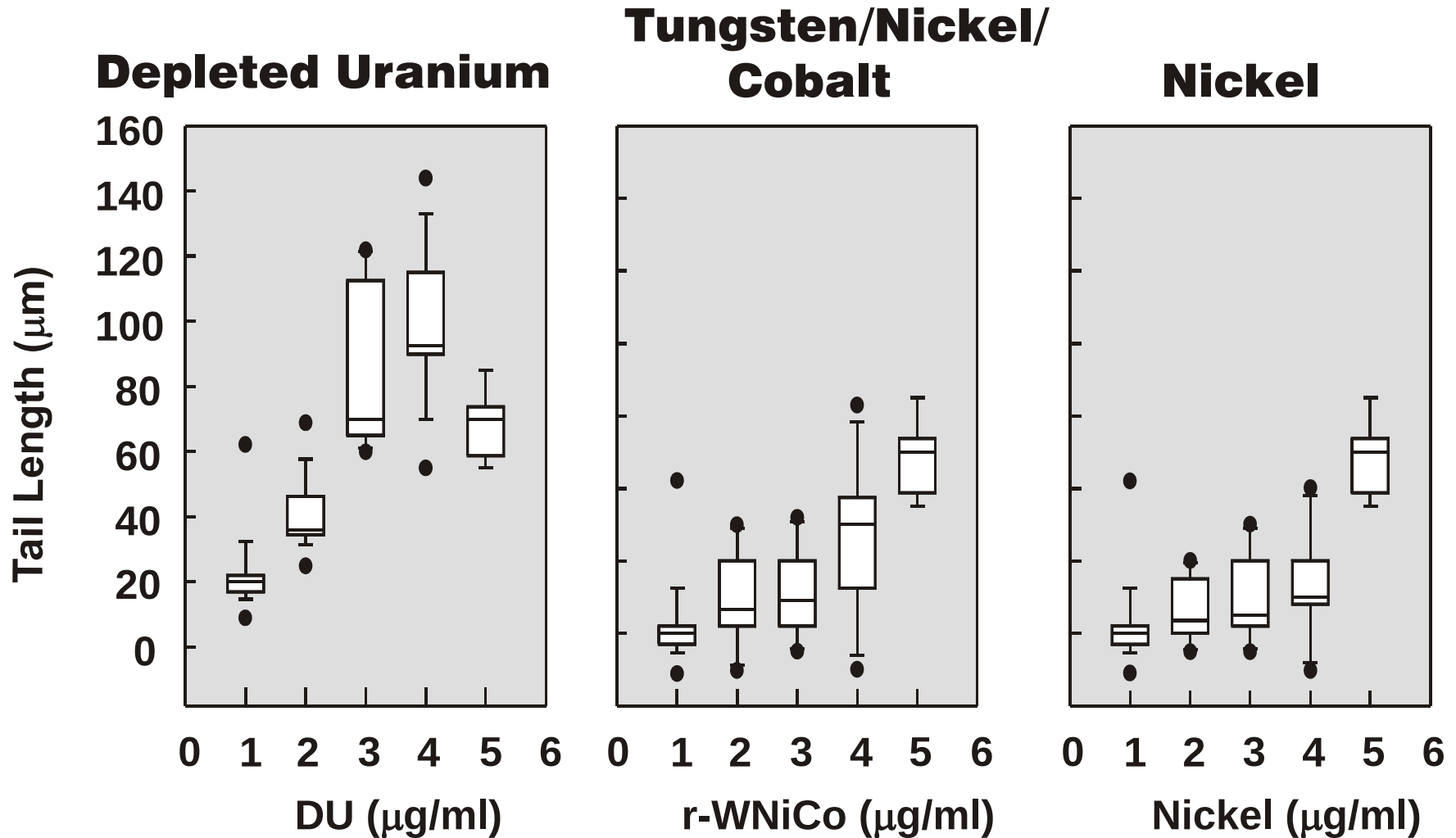
BEP2D Karyotype



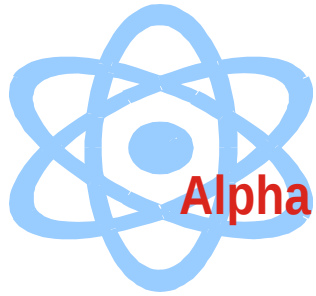
Tumorigenic Karyotype

# Genotoxicity

## Single Cell Gel Electrophoresis Assay - "Comet" Assay



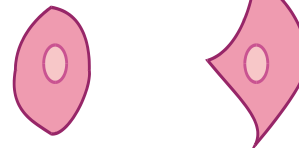
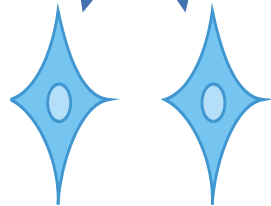
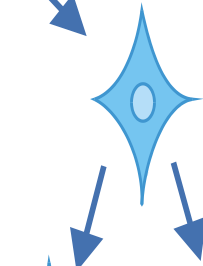
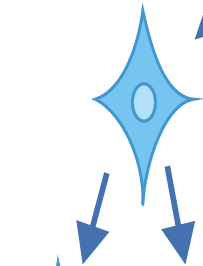
# Genomic Instability



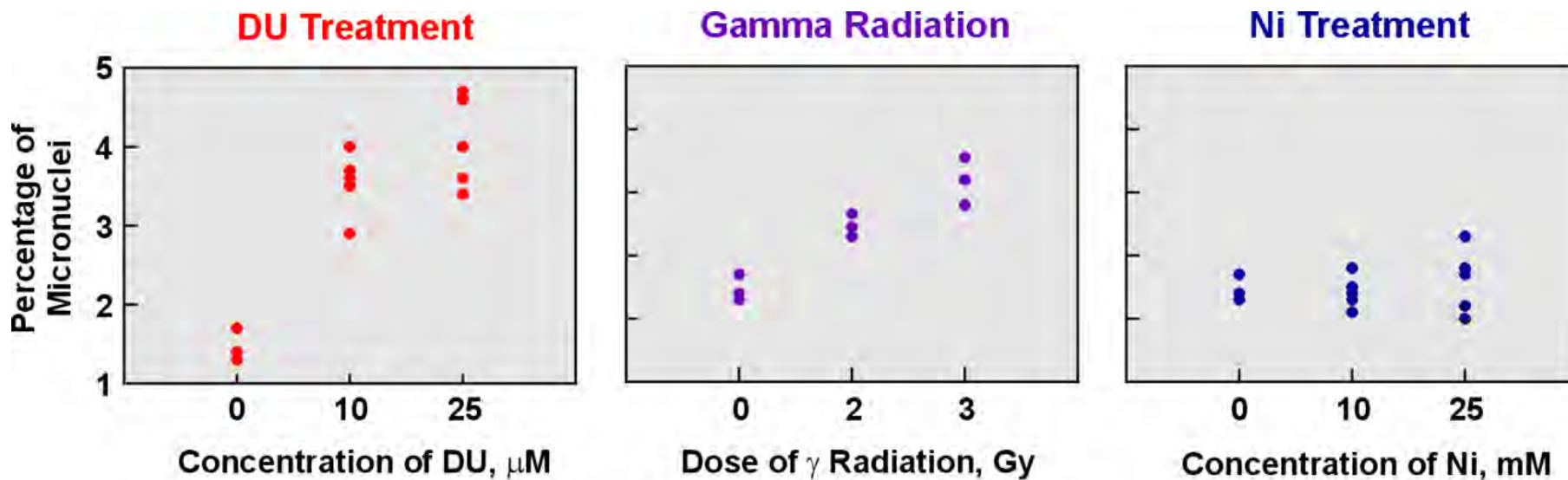
Alpha Particle



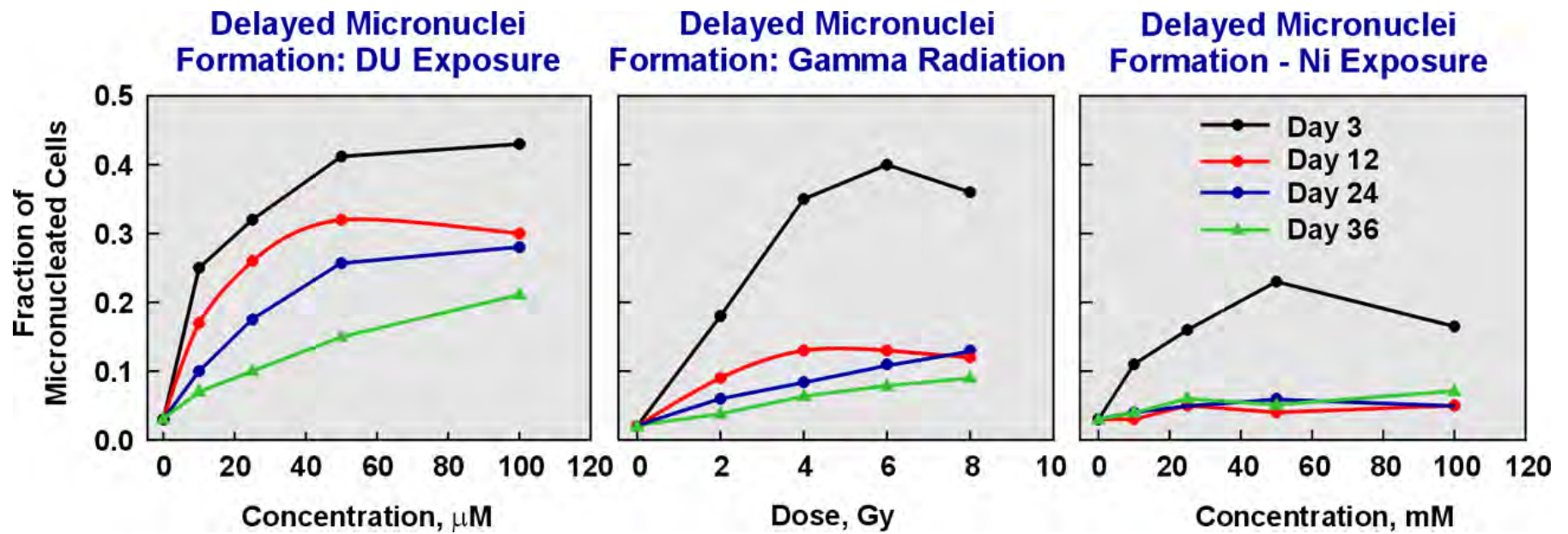
## Genomic Instability



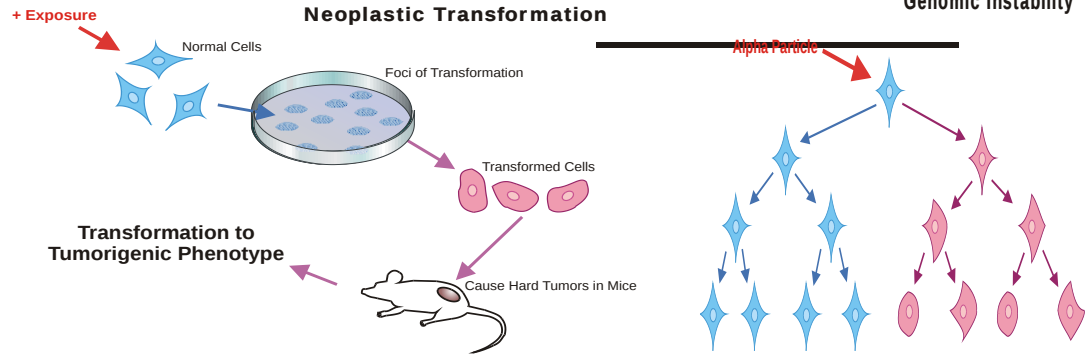
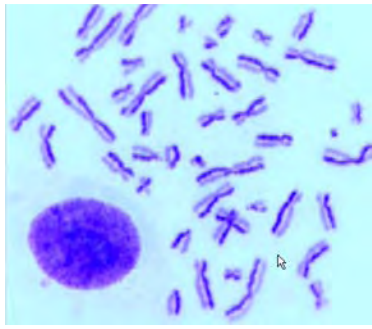
# Induction of Genomic Instability



Miller *et al*, *Journal of Environmental Radioactivity*, 2003;64(2-3):247-59.

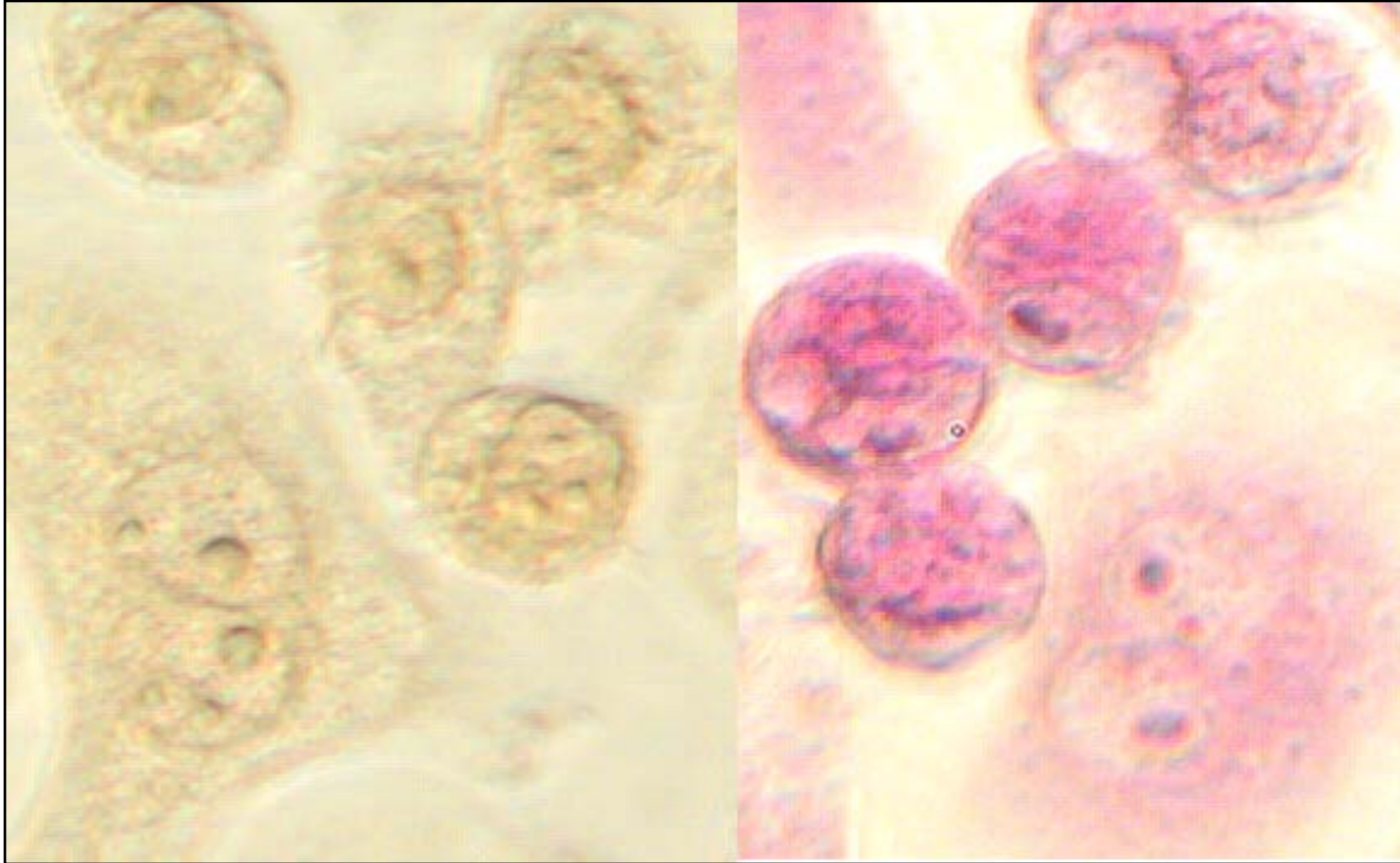


## Relative Comparison of DU, Nickel, and Alpha Particles



# **Molecular and Cellular Effects of DU**

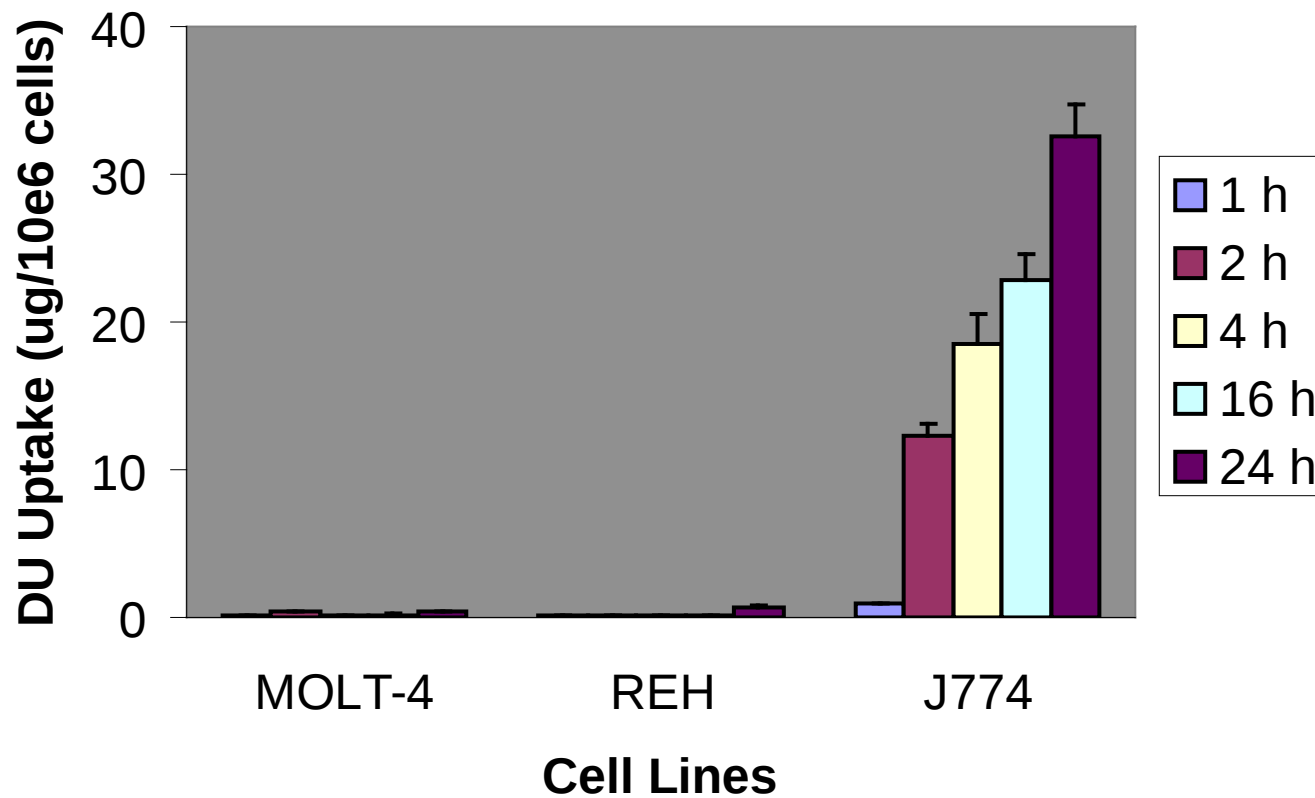
## PADAP Staining of DU-treated J774 Cells



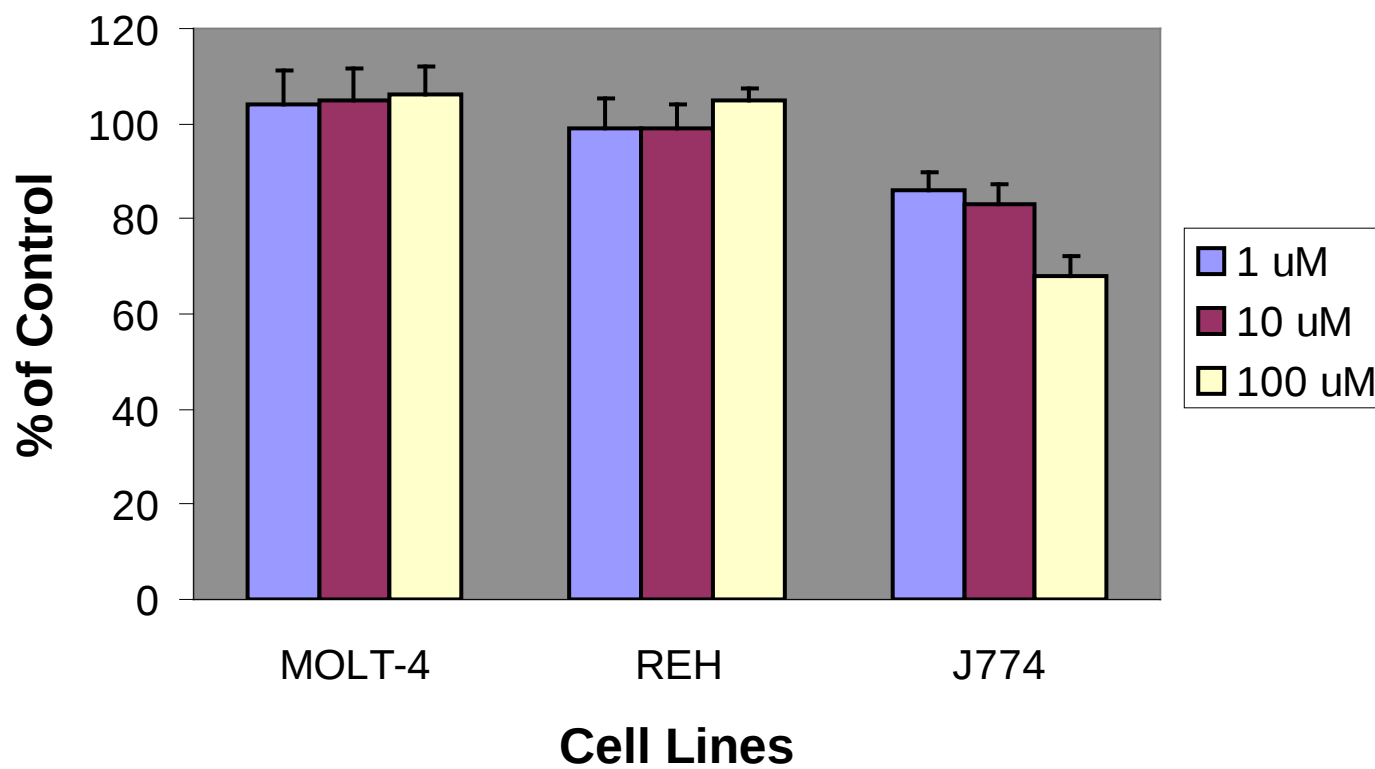
Without DU

With DU

## DU Uptake by Cultured Immune Cells

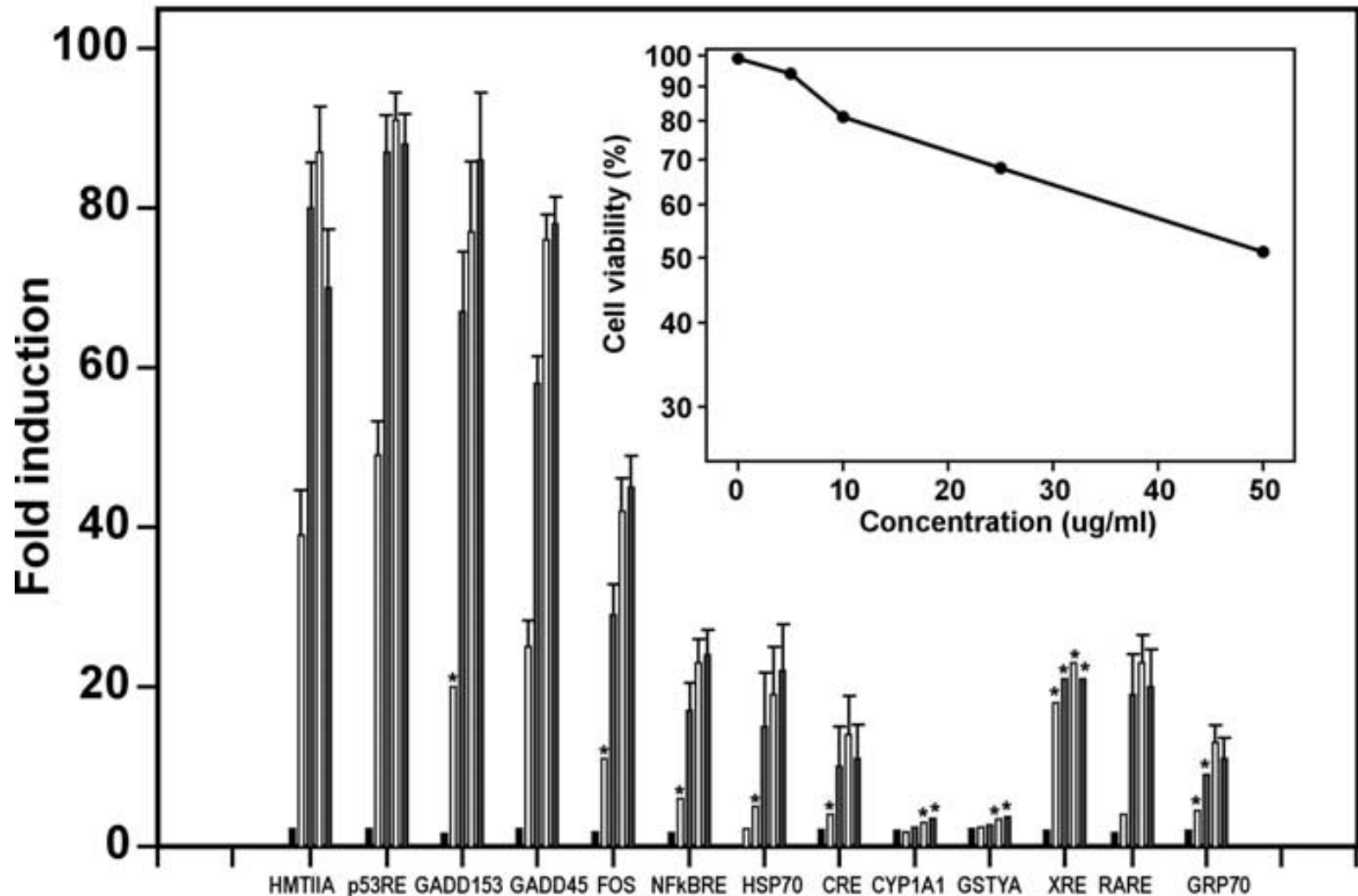


## Effect of DU on Cell Viability



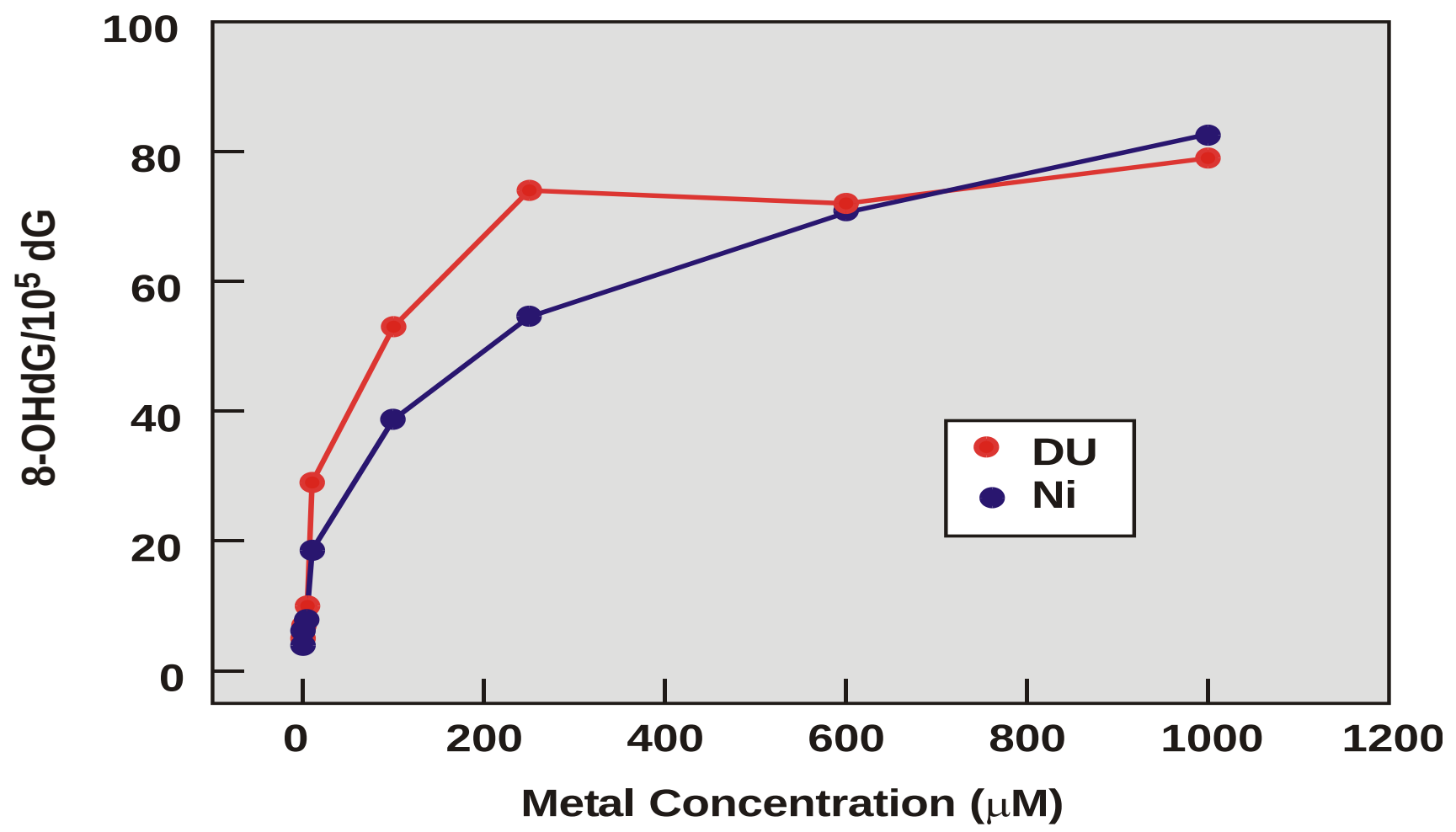
# DU Effects on Gene Expression

## Depleted Uranium



# Role of Oxidative DNA Damage in Human Cells

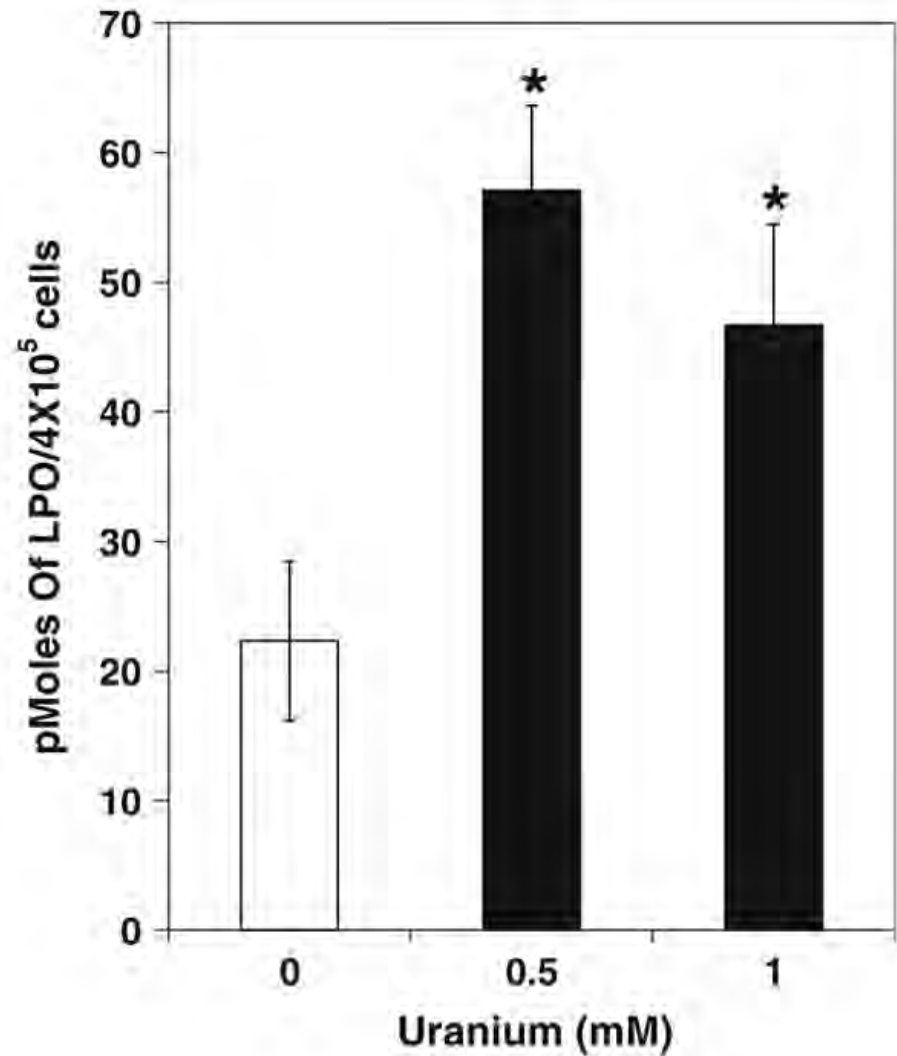
## Formation of 8-OHdG in DNA



Miller AC, et al, 2002, *J Inorg Biochem*

# DU Induces Oxidative Stress

Rat lung epithelial cells  
Reduction in GSH  
Reduction in SOD



# **Radiation versus Chemical Effects**

# Does DU Cause Radiation Specific Damage?

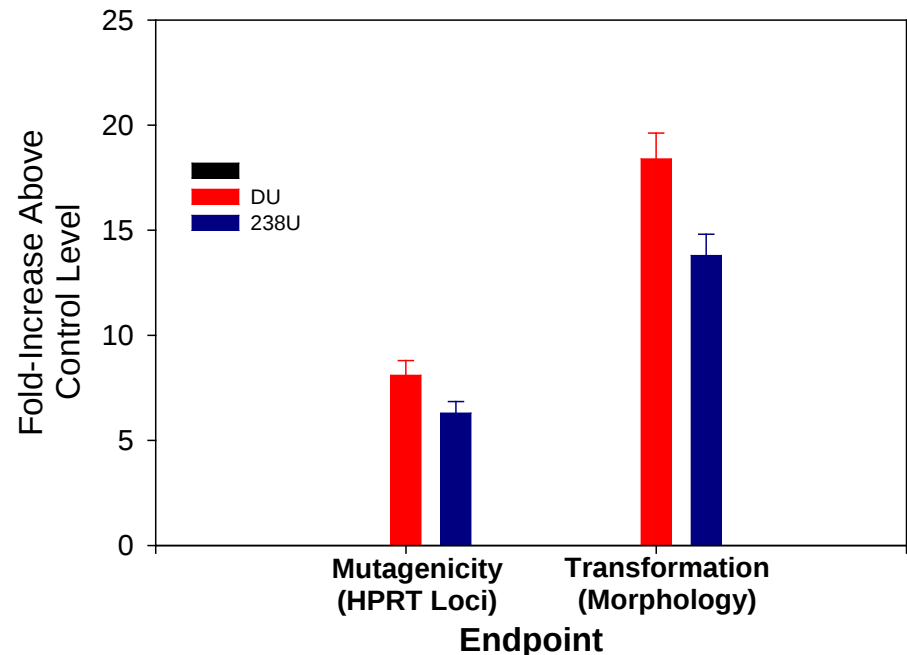
## Radiation Effects of DU: *In vitro* studies Two Approaches

1. Radiation-specific Damage -  
Dicentric Chromosomes



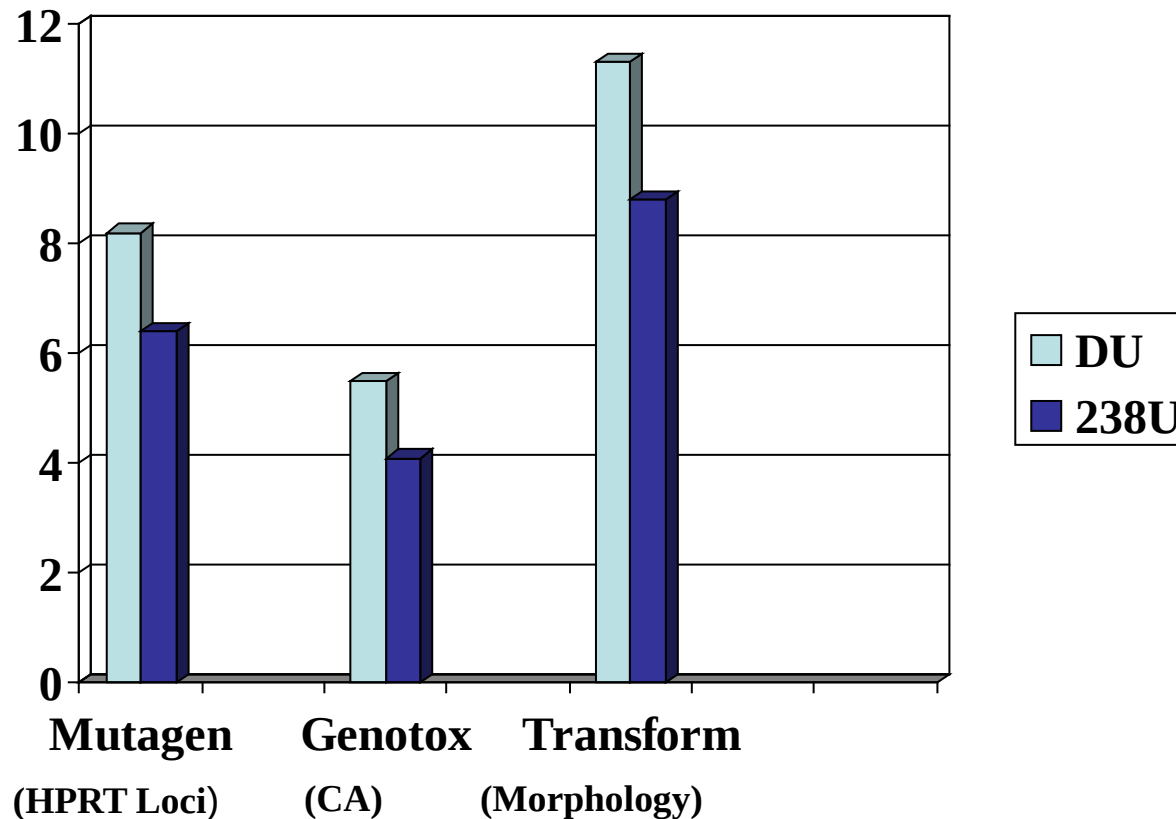
2. Uranium Isotope Comparison at Equal  
Chemical Concentration

| <u>Uranium Isotopes:</u> | <u>Rad Activity</u> | <u>Chem Tox</u> |
|--------------------------|---------------------|-----------------|
| <b>DU</b>                | <b>0.43</b>         | <b>1.0</b>      |
| $^{238}\text{U}$         | 0.33                | 1.0             |



Miller, *et al.*, *Radiat Prot Dosimetry*, 99(1-4):275-8, 2002  
Miller *et al.*, *Radiation Measurements*, 42:6-7:1090, 2007.

# Radiation Specific Effects *in Vitro*: Heavy Metal Mutagenicity, Genotoxicity Neoplastic Transformation: Comparison of DU and $^{238}\text{U}$ at Equal Concentrations



Miller, *et al*, *Environmental Health Persp*, Vol. 106, 1998

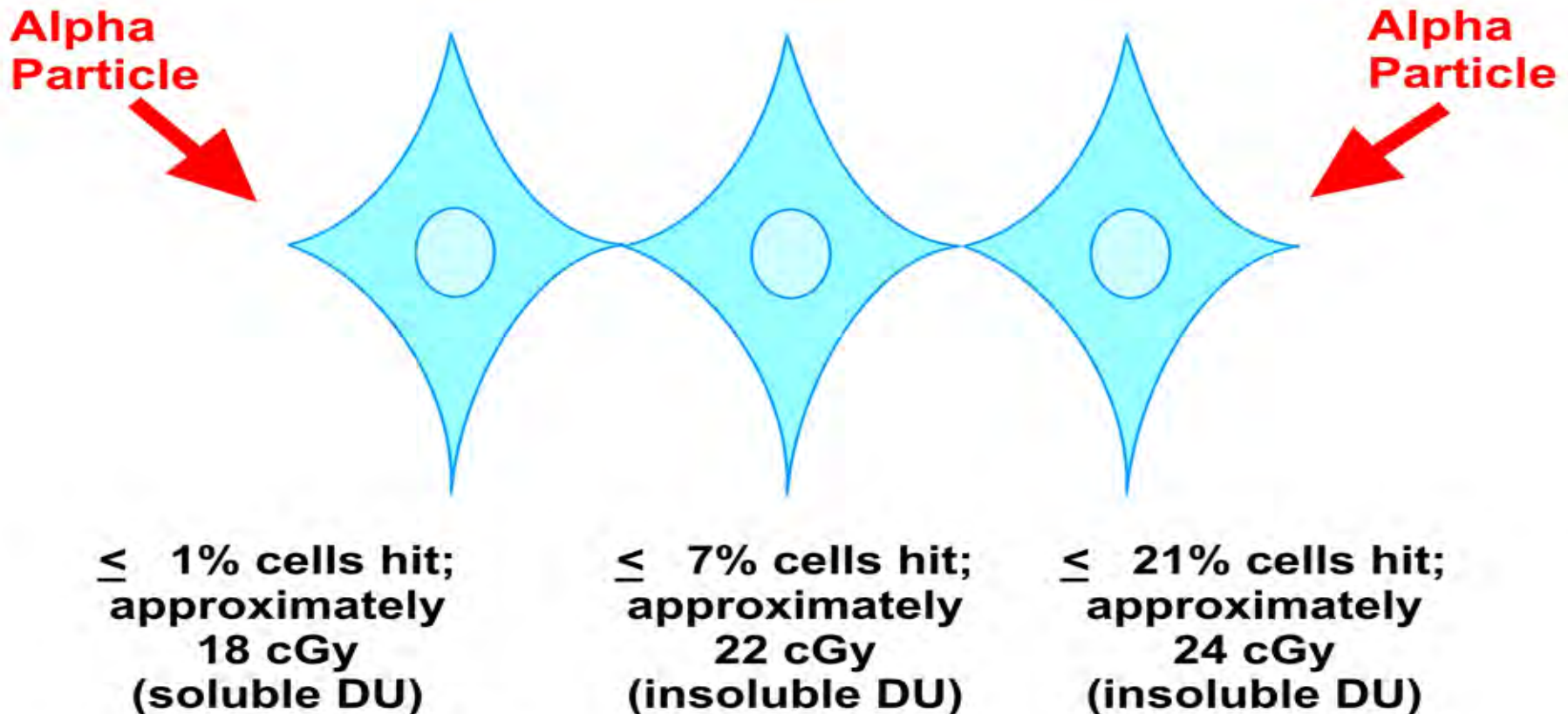
Miller, *et al*, *Carcinogenesis*, Vol. 22, 2001.

Unpublished data.

Miller 44

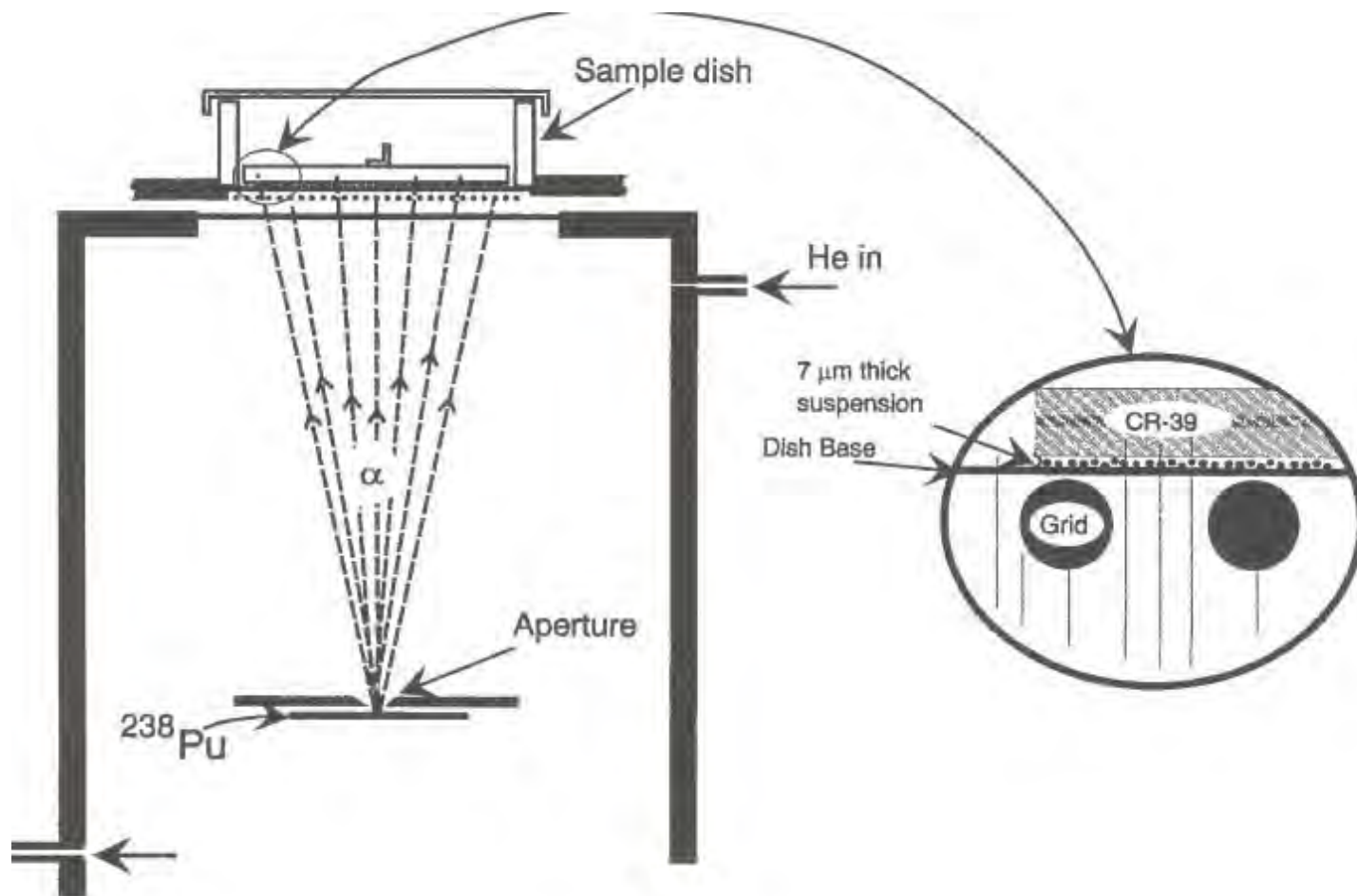
| <u>Uranium Isotopes:</u> | <u>Specific Activity</u> |
|--------------------------|--------------------------|
| $^{235}\text{U}$         | 2.2                      |
| DU                       | 0.43                     |
| $^{238}\text{U}$         | 0.33                     |

# **Third Approach: Mimic Radiation Dose from DU Radiation Dose Measurement "Microdosimetry"**



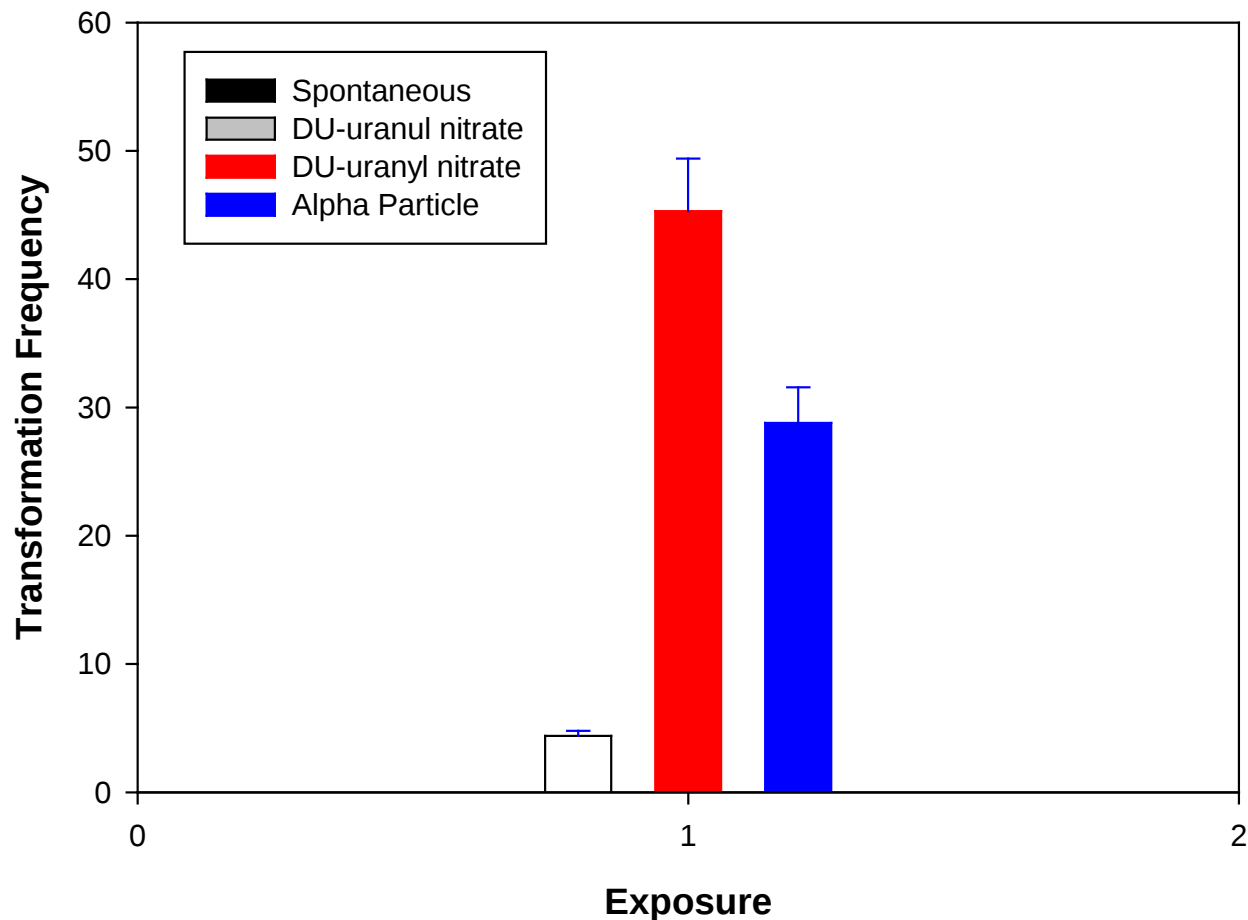
# Third Approach:

## Schematic Diagram of Alpha-Particle Irradiator: Shielding Effect of Interposing Grid Between Source and Cells



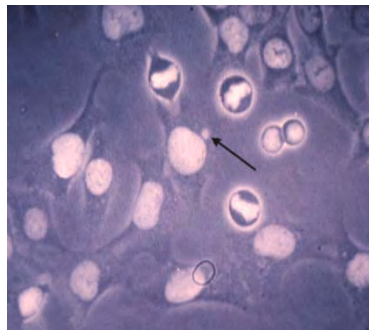
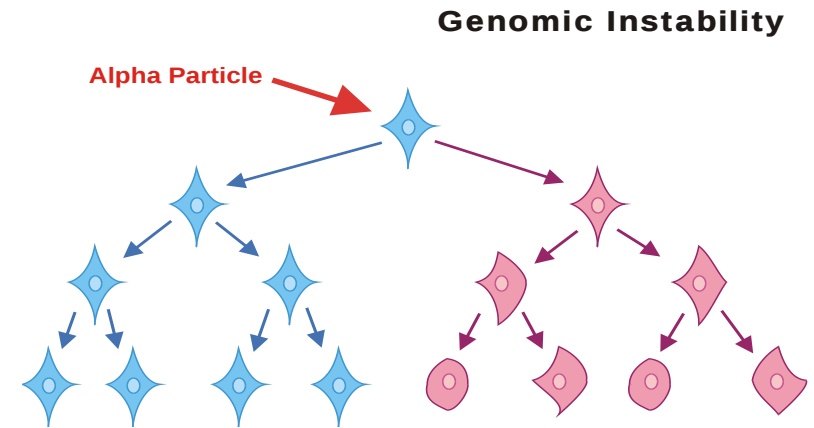
# Comparison of Alpha Particle Exposure from DU To Alpha Particles from Alpha Source

**17% Cell Nuclei Traversed by Alpha Particle from Either Source**

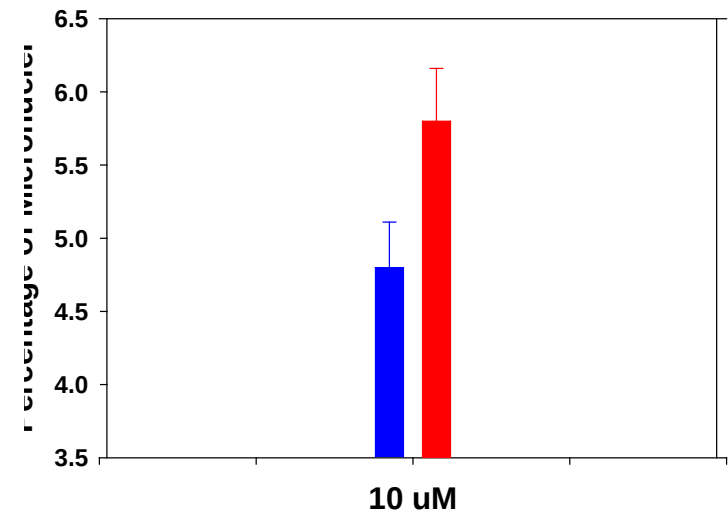


# Third Example of DU Radiation Effects: Genomic Instability

| <u>Uranium Isotopes:</u> | <u>Rad Activity</u> | <u>Chem Tox</u> |
|--------------------------|---------------------|-----------------|
| <b>DU</b>                | <b>0.43</b>         | <b>1.0</b>      |
| $^{238}\text{U}$         | 0.33                | 1.0             |



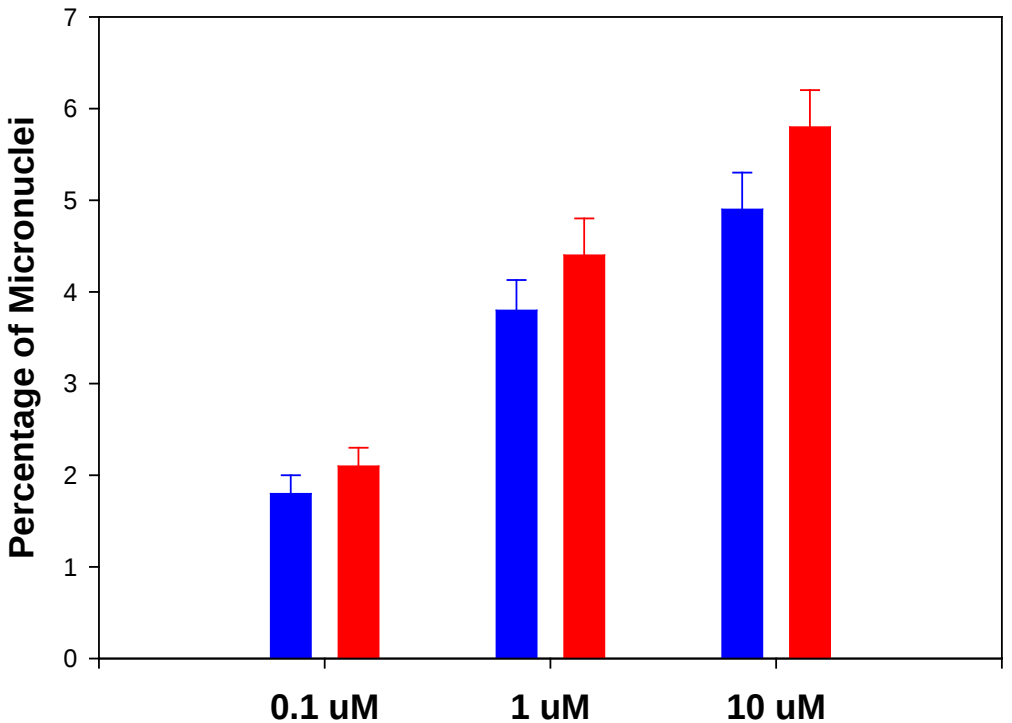
Number of Clones Tested (20)



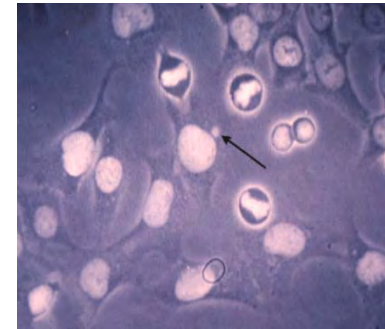
Special thanks to Gwen Watson, MRC UK

# Micronuclei as Endpoint of Genomic Instability Due to Radiation Effect

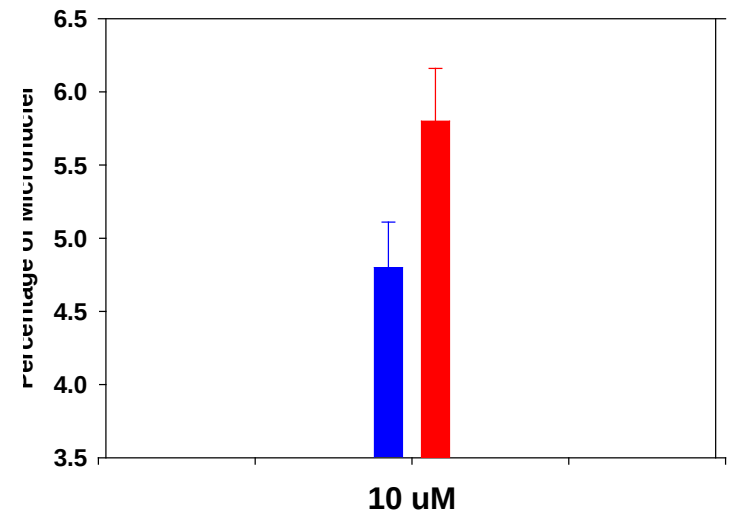
Number of Clones Tested (5-7)



| <u>Uranium Isotopes:</u> | <u>Rad Activity</u> | <u>Chem Tox</u> |
|--------------------------|---------------------|-----------------|
| <b>DU</b>                | <b>0.43</b>         | <b>1.0</b>      |
| $^{238}\text{U}$         | <b>0.33</b>         | <b>1.0</b>      |



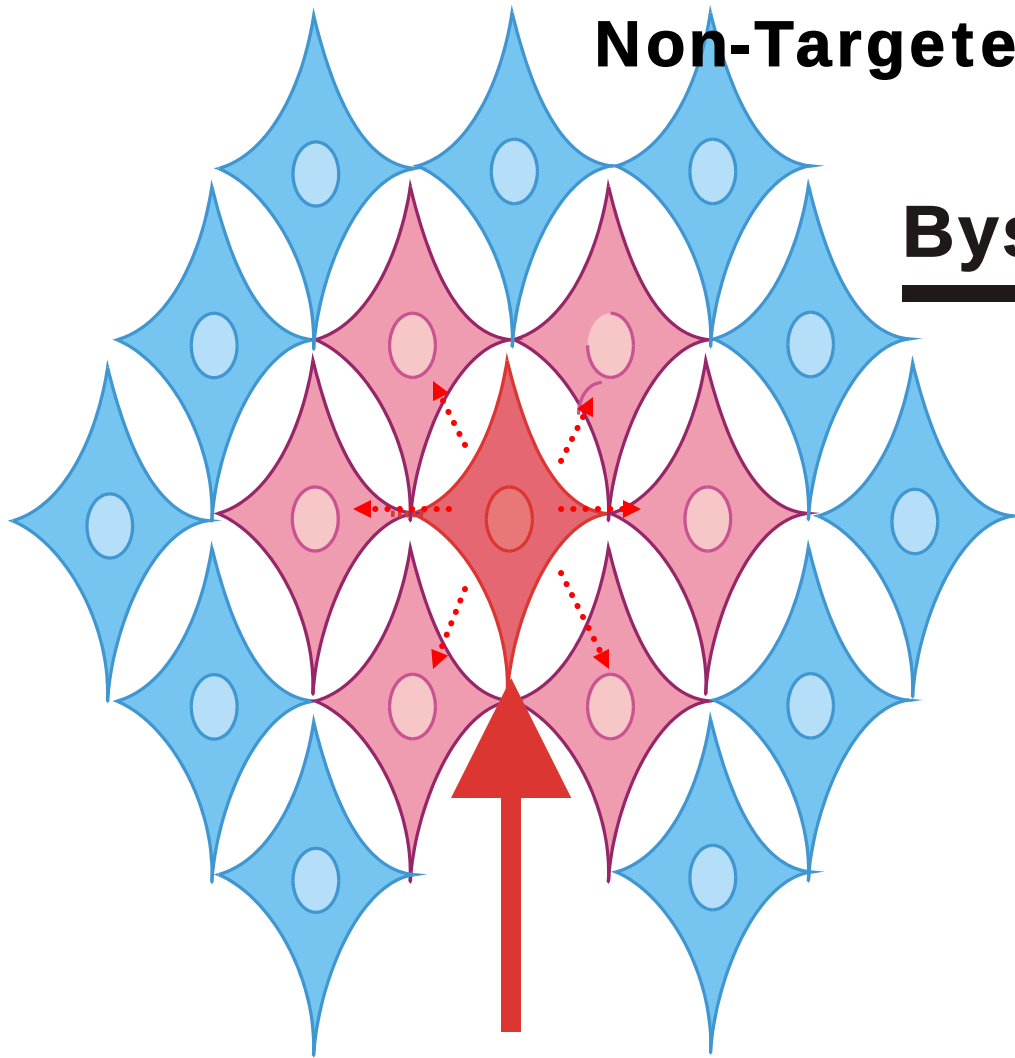
Number of Clones Tested (20)



Special thanks to Gwen Watson, MRC UK

# Non-Targeted Radiation Effect

## Bystander Effects

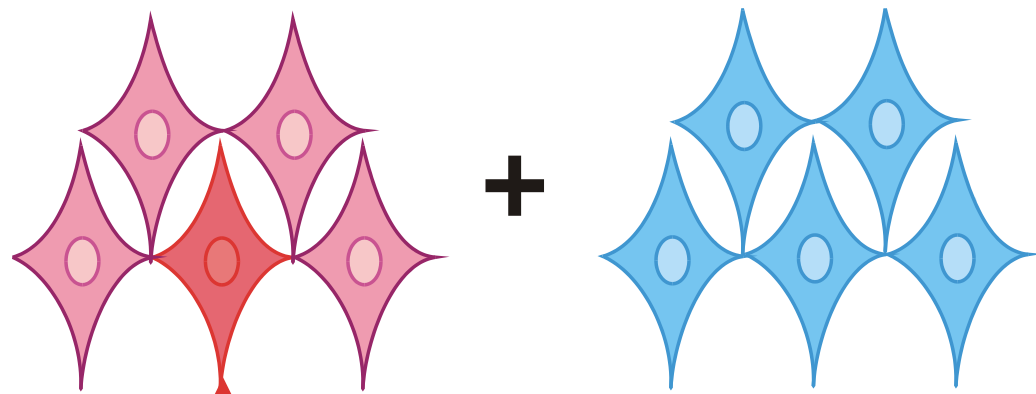


**Alpha Particle**

**1 cell hit but > 2 cells affected**

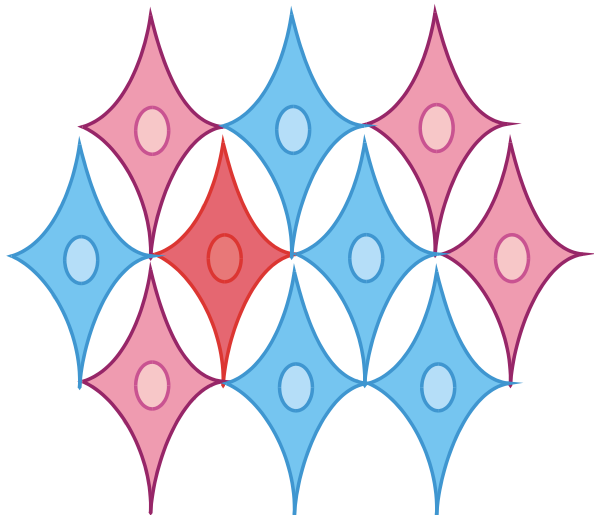
# **Bystander effects have been reported for a variety of endpoints using single-cell systems**

- ✓ **Mutation induction**
- ✓ ***In-vitro* oncogenic transformation**
- ✓ **Changes in gene expression**
- ✓ **Altered cell growth**
- ✓ **Sister-chromatid exchanges**
- ✓ **Cell killing (mitotic and apoptotic)**
- ✓ **Micronucleus induction**



DU Exposure

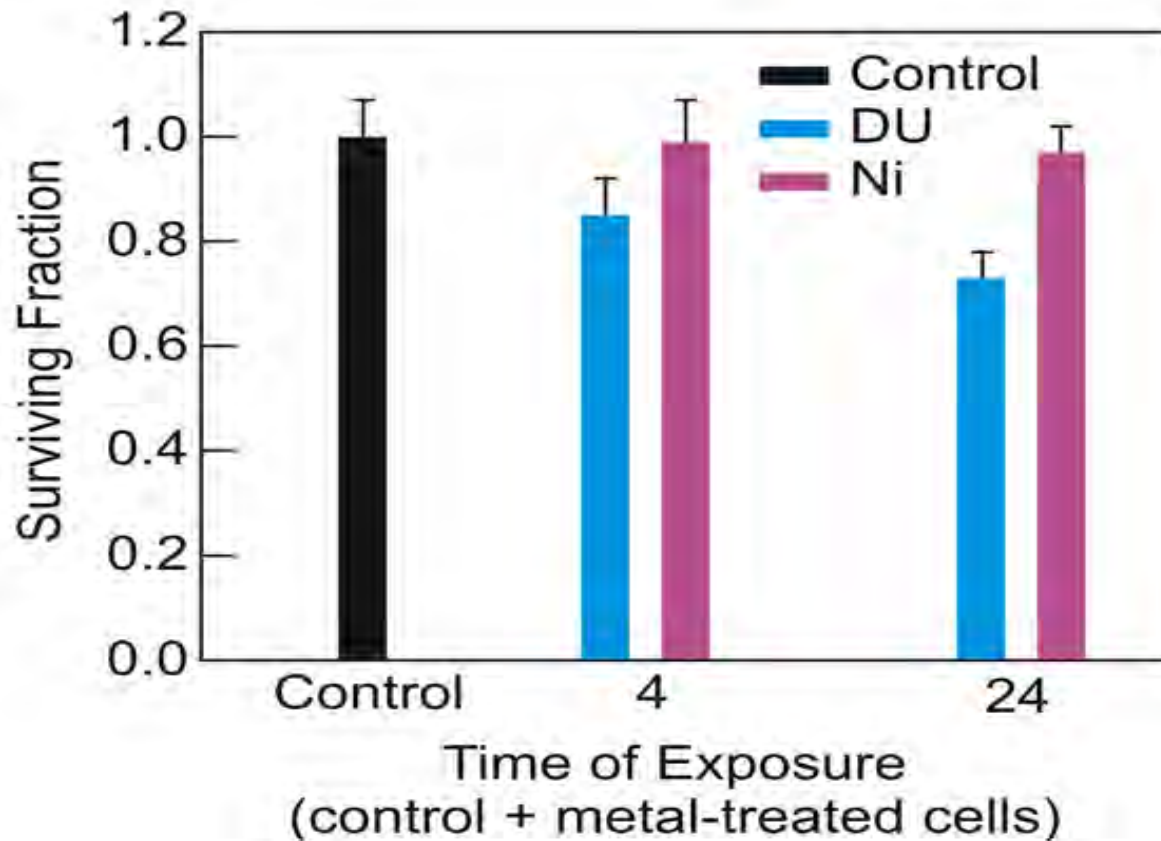
Rinse Cells



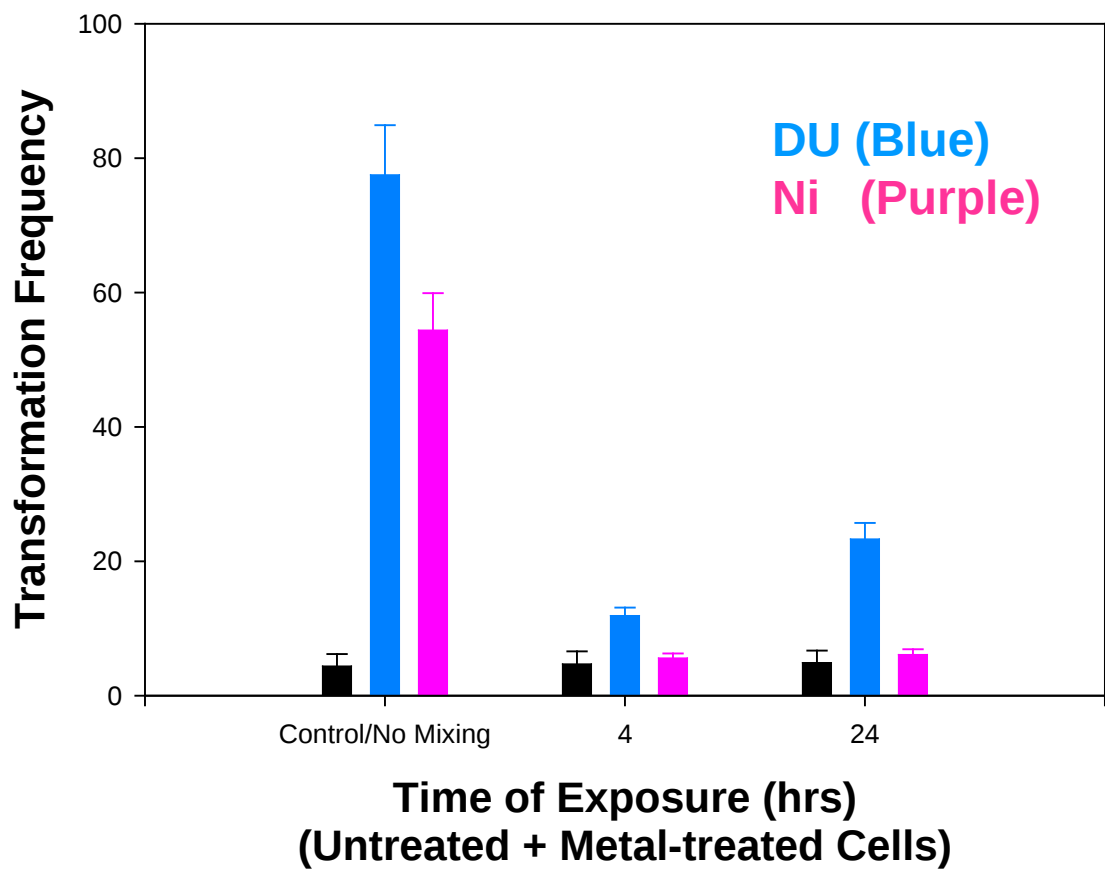
## Mixed Populations Analysis

---

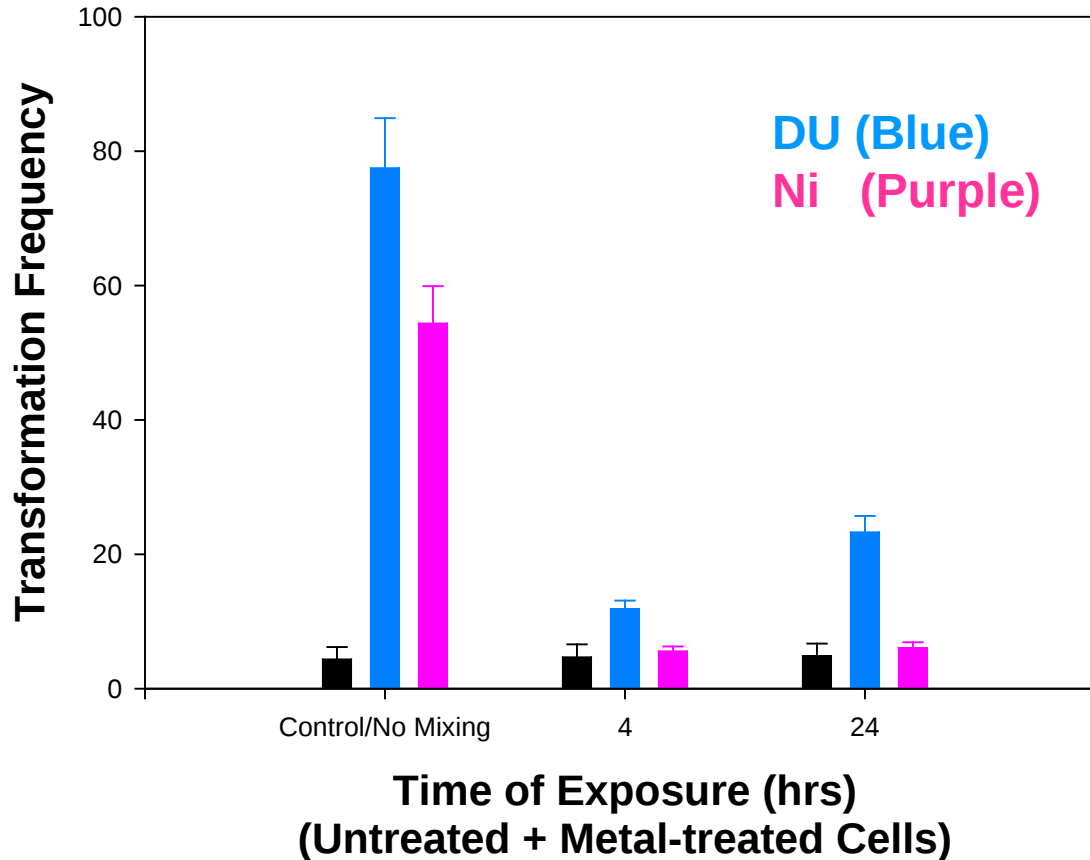
# Surviving Fraction of Bystander HOS Cells Co-cultured with HOS Cells Exposed to Heavy Metal



# Transformation Frequency of Bystander HOS Cells Co-cultured with HOS Cells Exposed to Heavy Metal



# Transformation Frequency of Bystander HOS Cells Co-cultured with HOS Cells Exposed to Heavy Metal



# Bystander Effects



**So yes, beware thy neighbor**

# DU Exposure

```
graph TD;
    A[DU Exposure] --> B[Adaptive response];
    A --> C[Neoplastic transformation];
    A --> D[Mutagenicity];
    A --> E[Cell damage and repair];
    A --> F[Cell death];
    B --> B1[No pathology];
    B --> B2[Altered gene expression];
    B --> B3[Cellular reorganization];
    C --> C1[Transformation];
    C --> C2[Oncogenes/tumor suppressors];
    D --> D1[Enhanced mutagenicity];
    E --> E1[Acute pathology];
    E --> E2[Toxicity assays];
    E --> E3[DNA damage];
    E --> E4[Cytogeneticity];
    E --> E5[Genomic instability];
    F --> F1[Acute pathology];
    F --> F2[Cell survival assay];
```

## Adaptive response

- No pathology
- Altered gene expression
- Cellular reorganization

## Neoplastic transformation

- Transformation
- Oncogenes/tumor suppressors

## Mutagenicity

- Enhanced mutagenicity

## Cell death

- Acute pathology
- Cell survival assay

## Cell damage and repair

- Acute pathology
- Toxicity assays
- DNA damage
- Cytogeneticity
- Genomic instability

## Other studies *in Vitro*:

1. **DU induces kidney cell toxicity *in vitro*.** Goldman et al, 2006 , “Nephrotoxicity of uranyl acetate: effect on rat kidney brush border membrane vesicles”. *Archives Toxicology* Jul;80(7):387-93
2. **DU induces neurotoxicity *in vitro*.** Aschner et al., 2006, “Neurotoxicity of depleted uranium: reasons for increased concern”. *Biol Trace Elem Res.*, Apr;110(1):1-17.
3. **DU induces immune toxicity in macrophages.** Wan B et al, 2006, “In vitro immune toxicity of depleted uranium: effects on murine macrophages, CD4+ T cells, and gene expression profiles. *Environ Health Perspect.* Jan;114(1):85-91.
4. **DU cytotoxicity is associated with mitochondrial/lysosomal toxicity by the reduced biological metabolites and ROS.** Pourahmad, et al. 2006, *Environmental Toxicol*, Aug;21(4):349-54
5. **DU is absorbed by intestinal cells but is not toxic.** Dublineau I, et al, 2006, *Toxicology*. 227(3):227-39.
6. **Suppression of DU-Induced Transformation Can be Achieved Pharmacologically Using Phenyl Fatty Acids,** Miller AC, et al, 2001, “Suppression of DU-Induced Neoplastic Transformation. *Radiat Res.* 2001 Jan;155(1 Pt 2):163-170.

## **Conclusions *in Vitro*:**

- 1. DU induces neoplastic transformation, mutagenicity, and genotoxicity *in vitro*.**
- 2. DU is involved in uranium-induced genomic instability.**
- 3. Alpha particles similar in energy and distribution to those resulting from cellular uranium exposure to DU are sufficient to transform cells.**
- 4. Radiation bystander effects are involved in uranium-induced neoplastic transformation and genomic instability.**

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