The Unique Vulnerability and Resilience of Developing Organisms to the Exposure to Environmental Toxicants: Evaluating adult and children’s sensitivity to Environmental Toxicants

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A Historical Perspective

Science and Society does not have a perfect record in correctly judging the risks of drugs, chemicals and other environmental agents. Beneficial agents have been delayed or rejected and hazardous agents have been approved and accepted. These misjudgements have been due to poor science, lay or political pressure groups and public fear.

Let us hope that our deliberations will be based primarily on good science.
Environmental Agents Alleged to Increase the Risk of Cancer

- Chlorination
- Fluoridation
- The Cranberry Caper
- Alar
- Cyclamates
- Saccharin
- Pesticides
- Trace Amounts of Heavy Metals
- Chlorinated Hydrocarbons i.e. TCMeth, etc.
- Microwave Radiation
- Ultrasonic Radiation
- Electromagnetic Fields

Environmental agents that cause cancer or death

- Cigarettes
- Alcohol
- Auomobile
"I think it is absolutely essential that we do not delude ourselves about the magnitude and complexity of our task. The general public is easily scared and when they are scared, they may form pressure groups to push governmental agencies into action. These agencies are scientifically naive and have to rely on our advice. We should be very careful not to give advice that is itself naive; that is advice based on oversimplified tests and facile interpretations." (Auerbach 1971)
Diseases Of Affliction

Through the ages:

- Cancer
- Mental retardation
- Psychiatric illness
- Hereditary diseases
- Congenital malformations
- Reproductive loss

Brent Nemours Foundation
The Goals of this Presentation

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2. To examine the thesis that children are more vulnerable and sensitive to environmental toxicants.

3. To utilize the methods of evaluating scientific studies in order to estimate human risks from exposures to environmental toxicants. From what studies can you determine human risks?

4. What are the soluble and insoluble problems that we have to face.
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Risks of Postconception (Intrauterine) Exposure to Reproductive Toxicants
(Threshold effects, dose and agent related risks)

- Pregnancy loss (early or late abortion)
- Congenital malformations.
- Stillbirths
- Growth retardation
- Prematurity
- Behavioral or neurological effects
- Cancer (stochastic phenomenon)

There are over 50 drugs, chemicals and physical agents that are teratogenic or are reproductive toxins.
Dose Response Relationship of Reproductive Toxins As Compared To Mutagens And Carcinogens

Percentage of survivors with reproductive toxicity

Risk of Teratogenesis

Risk of Mutagenesis

Background Incidence of Human Reproductive Toxicity, Birth Defects, Spontaneous Abortion & Genetic Diseases

Dose of Teratogen or Mutagen
Stochastic and threshold dose-response relationships of diseases produced by environmental agents*

<table>
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<tr>
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<th>Diseases</th>
<th>Risk</th>
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* Modified from Brent.1987a,b, 1990a,b.

Nemours
# Vulnerability of Various Stages of Embryonic Development to Acute Exposures

1) First two weeks post conception: The all-or-none period

2) Organogenesis: 16th to 40th post-conception day. Major malformations of the brain, eyes, ears, limbs, lungs, heart, kidneys, some craniofacial malformations, neural tube defects, deafness, eye malformations, autism, absent corpus callosum, etc.

3) Early fetogenesis: 40th day-60th day, cleft palate, microphthalmia, hydrocephalus

4) Midgestation: 8th to 15th week. Interference with neuron proliferation, differentiation and migration, brain and skull size, fetal growth, genital growth retardation, microcephaly, mental retardation, ?epilepsy.

5) Late fetal development: susceptible to alterations in CNS maturation and growth, fetal growth retardation or growth retardation of specific organs, effects on the CNS, i.e., cerebral palsy, epilepsy, ADHD, psychiatric disorders, infarcts, congenital strokes, mental retardation, neurological abnormalities.
Pre differentiation Period

Period of Early Differentiation

Period of Advanced Organogenensis

Usually Not Susceptible to Teratogenesis

Highly Susceptible to Teratogenesis

Increasingly Resistant to Teratogenesis With Increasing Age
### Human Developmental Stages Sensitive to the Production of Malformations by Thalidomide (Brent and Holmes 1988)

<table>
<thead>
<tr>
<th>Developmental Stage (Days)</th>
<th>Limb or other Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-24</td>
<td>Microtia</td>
</tr>
<tr>
<td>24-29</td>
<td>Amelia, upper limbs</td>
</tr>
<tr>
<td>21-26</td>
<td>Thumb aplasia</td>
</tr>
<tr>
<td>24-33</td>
<td>Phocomelia, upper limbs</td>
</tr>
<tr>
<td>23-34</td>
<td>Hip dislocation</td>
</tr>
<tr>
<td>27-31</td>
<td>Amelia, lower limb</td>
</tr>
<tr>
<td>25-31</td>
<td>Preaxial aplasia, upper limb</td>
</tr>
<tr>
<td>28-33</td>
<td>Preaxial aplasia, lower limb</td>
</tr>
<tr>
<td>28-33</td>
<td>Phocomelia, lower limb, Femoral and girdle hypoplasia</td>
</tr>
<tr>
<td>33-36</td>
<td>Triphalangeal thumb</td>
</tr>
</tbody>
</table>
Developmental vulnerabilities of the infant, child and adolescent
The developmental events that can be affected by drugs, chemicals and physical agents include the following developmental events that occur during infant, childhood and adolescent development.

1. Interference with growth, epiphyseal development and epiphyseal closure.
2. Reproductive, fertility, endocrine and hormonal effects.
3. Alteration of the adequacy of the adult immune system.
4. Neurobehavioral, neurological effects.
5. Cancer.
Developmental vulnerabilities of the infant, child and adolescent

While there is an immense amount of information about the vulnerability of the embryo and fetus at various stages of development, there is much less quantitative and qualitative data pertaining to the vulnerability of the infant, child and adolescent. We can make some educated guesses, which indicates how much more primitive our data is with regard to postnatal developmental vulnerability.
Developmental vulnerabilities of the infant, child and adolescent

- CNS
- Lymph
- Ionizing radiation induced cancer
- Impact of Hypothyroidism and Sensitivity to I-131

Increasing vulnerability

Age (years)

Nemours
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Children Are Different.

There are many diseases that occur only in children or predominantly in children.

Could the risk of any of these diseases be affected by environmental toxicant exposures?
Children’s Diseases

- Adenocarcinoma of the vagina during adolescence from prenatal DES exposure?
- Acute lymphatic leukemia
- Ewing’s Sarcoma
- Wilms’ Tumor
- Osteogenic Sarcoma
- Medulloblastoma
- Neuroblastoma
- Retinoblastoma
- Bronchiolitis
- Caloric insufficiency due to Failure to Thrive resulting in neurocognitive impairment
- Cow’s Milk Allergy
- Craniosynostosis
- Group B Strep Sepsis, pneumonia and osteomyelitis
- Henoch Schönlein Purpura
- Idiopathic Intussusception
Children’s Diseases

- Infant Botulism
- Kernicterus
- Colic
- Mental retardation due to hypothyroidism
- Necrotizing Enterocolitis
- Croup
- Febrile Seizures
- Disuse Amblyopia
- Pyloric Stenosis
- Respiratory Distress Syndrome
- Retinopathy of Prematurity
- Salter Harris Fracture
- Sudden Infant Death Syndrome
- Transient Tachypnea of the Newborn
- Impaired language development due to deafness
- Increased susceptibility to caries due to ETS
Children Are Different.

Children may be more or less sensitive to environmental toxicants and may have better resiliency from exposures to environmental toxicants when exposed to low exposures.

There is data that indicates that young children are more sensitive to the oncogenic effects of ionizing radiation.
Developing Organisms are Different

The facts clearly indicate that developing organisms are different than adults. However, few generalizations about children’s vulnerability to environmental exposures apply, given that vulnerability and sensitivity are specific to the embryo and child’s developmental stage, and is also agent specific.
The newborn or infant animal was more sensitive to many drugs (chloramphenicol, morphine, some other opiates, picrotoxin, tetracycline, novobiocin, some organophosphate anticholinesterases, atropine, histamine, sodium salicylate) and less sensitive to others (ethanol, strychnine, metrazol, codeine, acetyl-cycloheximide, thiourea, thyroid hormone). Many other drugs have sensitivities that were similar in the neonate and adult animal.
It is also important to note that children and adolescents have better recuperative capacities than adults. This means that for some exposures, the young can recover from some effects more rapidly and completely than adults.
While this is an optimistic view, Done (1964) pointed out, that although the number of drug hazards that have proven to be unique in the infant has proven to be small,

“Without exception, recognition of a proven hazard has come about only after widespread use, and then usually when tragic consequences focused attention on the drug” (Done 1964).
Cancer
Dose Response Relationship Of Environmental Toxicants As Compared To Mutagens And Carcinogens

Risk of Mutagenesis

Risk of a Toxic Effect

Dose of Toxic Agent or Mutagen

100 %

0

Risk of Toxic Effect

Brent-Nemours
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Evaluating The Allegation Of Environmental Agent Toxicity
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1. Consistency of epidemiological studies
2. Secular trend analysis
3. Animal reproductive studies
4. Dose response relationships and pharmacokinetic, and toxicokinetic studies comparing human and animal metabolism and effects.
5. In vitro studies
6. Biological plausibility
   a. Mechanism of action studies
   b. Receptor studies
   c. Nature of the effects
   d. Biologic principles
   e. Biologic plausibility
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## Types of Epidemiological Studies

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Accuracy</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort Study</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Case Control Study</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cluster</td>
<td>+/-</td>
<td>++++</td>
</tr>
<tr>
<td>Isolated Case Report</td>
<td>-</td>
<td>++++</td>
</tr>
</tbody>
</table>
The difficulties inherent in EMF epidemiological studies

1. Documentation and measuring exposure in the “exposed” and “control” groups is inexact compared to drug studies and chemical exposure studies.

2. An expectation by the public, news media and some scientists that all epidemiological studies have to be negative in order to conclude that there is no measurable risk.
Evaluating The Allegation Of Environmental Toxicity

1. Consistency of epidemiological studies
2. **Secular trend analysis**
3. Animal reproductive studies
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## Overall Childhood Cancer Incidence, USA

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence per Million Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All childhood cancers</td>
</tr>
<tr>
<td></td>
<td>166 155 162 160 161 156 158 162 156 161</td>
</tr>
<tr>
<td></td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td></td>
<td>23.7 24.9 27.6 28.2 28.3</td>
</tr>
<tr>
<td></td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td></td>
<td>5.2 4.9 3.8 5.1 4.8</td>
</tr>
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Nemours
Evaluating The Allegation Of Environmental Toxicity

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Well-performed animal studies have important advantages.

1. The actual exposure can be determined
2. Multiple exposures can be utilized
3. The effects can be directly observed and recorded by the investigators,

Disadvantages are that

1. The animal model dosimetry may not be mimicked in the exposed humans.
Evaluating The Allegation Of Environmental Toxicity

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In vitro studies

When epidemiological studies indicate measurably increased risks from exposure to environmental toxicants, in vitro studies can assist in determining the mechanism of action and provide data that supports the epidemiological studies.

Rarely is it possible to determine human risks from in vitro studies without positive epidemiological findings.

Extensive programs using in vitro studies in the absence of positive epidemiological or positive well-performed animal studies is a waste of resources.
Evaluating The Allegation Of Environmental Toxicity

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Nature of the Effect that is of Concern

If adults manifest an oncogenic effect at a particular exposure, it is reasonable to question whether children will have a greater risk at that same exposure?

If you do not observe an oncogenic effect in adults from EMF exposure, would you expect children to manifest the effect because they are children and may be more sensitive?
Biological Plausibility

1. Electrical fields are used to fuse zygotes for embryo fusion experiments and to stimulate non-union fractures. These clinical exposures are very high. The results do not support the suggestion that very low exposures are cytotoxic or oncogenic.

2. EMF does not have specific capabilities of affecting the genomic or chromosome structure, because the energy of EMF and microwave photons cannot cause ionization in tissues.

3. Even when tissues are exposed to large doses, cell killing does not occur.

4. Natural and unavoidable thermal electric fields at the cellular level have current densities equivalent to those induced by a 60 Hz magnetic field of 6.5 G.

5. The earth's magnetic field, has zero frequency, unless one is accelerating through the field, i.e. flying in an airplane. The strength of the earth's field is approximately 450 mG.

6. ELF and EMF are markedly different in their ability to produce electrical currents in human and mammalian tissues. The resistance of the skin markedly reduces the impact of ELF.
Biological Plausibility: Biophysical Considerations in the microwave communication frequency ranges.

- **Thermal mechanisms:** Biological processes are sensitive to temperature and in some cases, rates of temperature rise.

- **Bulk temperature rise:** An SAR of 0.4 W/kg will produce a rate of temperature rise of $10^{-4}$ °C/sec in soft tissue. At this exposure it is unlikely that there will be any temperature rise.

- **Rate of temperature rise:** The ANSI/IEEE limits for brief pulses corresponds to a maximum absorbed energy of 28.8 J/kg, which would produce an incremental temperature rise of 0.007 per pulse in soft tissue.

- **Thermoelectric Expansion and Microwave Hearing:** Auditory stimuli that are elicited when a person’s head is exposed.

- Thermally-induced membrane phenomenon.
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Soluble and Insoluble Problems
Why Is There Such A Controversy Concerning The Reproductive Risks Of EMF?

Scientists can never say with certainty that an environmental agent has no deleterious effects. We can say that there does not appear to be an increase in effects or there are no measurable increases in these effects. This level of scientific uncertainty is not acceptable to some scientists, some segments of the public, the media or politicians.
EMF Controversy

There have been suggestions that the effects of EMF have been primarily negative because we may have missed the window of biological sensitivity for both the frequency and the intensity of the magnetic fields. There is a limitless combination of frequency and exposure that can never be tested.

This concept is magnified by the variability in modulated radiofrequency energy (pulse modulation and amplitude modulation and combinations of both types of communication microwaves). We will never be able to test the limitless combinations.
EMF Controversy

Results of the RERF studies of the Atomic bomb survivors reveals that children were more susceptible to the leukemogenic effect of high exposures to ionizing radiation than were adults, most likely due to radiation’s genotoxic effect.

But adults did develop cancer and leukemia from the radiation exposure.

What mechanisms could explain an oncogenic effect for EMF from microwave communication frequencies?
Mechanisms

Genotoxicity, mutagenicity
Increase cell proliferation
Cell killing
Conclusion
The clinical and biological data have been presented with regard to the different responses and sensitivity of developing organisms, namely the embryo and child, when compared to the adult. We have much better data on the sensitivity of various stages of embryonic development than we have about the sensitivity of the stages of children and adolescent’s development. But this lack of information should not deter us from attempting to arrive at definitive conclusions about the risk of EMF to children and adults.

1. Children’s sensitivity or resiliency is stage and agent specific.
2. Biological plausibility is an important issue in the evaluation of the risks of communication frequency microwaves.
3. Definitive conclusions cannot be based on hypotheses.

Nemours
Conclusion

The four introductory presentations will set the stage for discussions about the risks of EMF. We have an opportunity to learn from each other and hopefully arrive at a consensus concerning what information is necessary in order to arrive at a definitive conclusion as to whether there are measurable risks from EMF exposure and/or whether further analysis and research is necessary.
The End
Any Questions or Comments
Any Questions or Comments
### Stochastic and threshold dose-response relationships of diseases produced by environmental agents*

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Nemours
<table>
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<tr>
<th>Type</th>
<th>X-rays γ radiation</th>
<th>Ultrasound</th>
<th>Microwave Diathermy</th>
<th>EMF, 60Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
<td>Ionization, mutagenesis, carcinogenesis, teratogenesis</td>
<td>Compression, rarification, cavitation, tissue disruption, hyperthermia</td>
<td>Hyperthermia</td>
<td>Electrical and magnetic fields in tissue</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>Yes</td>
<td>No, Yes</td>
<td>No, Yes</td>
<td>No</td>
</tr>
<tr>
<td>DNA specificity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Phenomena</td>
<td>Stochastic Threshold</td>
<td>Threshold</td>
<td>Threshold</td>
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</tr>
</tbody>
</table>
Risk of Point Mutations Compared to the Risk of Cell Death in Rapidly Proliferating Cells
### Cancer Epidemiology: According to the National Cancer Institute

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new cancers diagnosed in the USA each year</td>
<td>1,200,000</td>
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<tr>
<td>Number of children and adolescents diagnosed in this population</td>
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</tr>
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<td>Annual incidence rate for all cancers</td>
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Biological Plausibility (EMF)

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2. EMF does not have specific capabilities of affecting the genomic or chromosome structure, because the energy of EMF and microwave photons cannot cause ionization in tissues.

3. Even when tissues are exposed to massive doses, cell killing does not occur.

4. Natural and unavoidable thermal electric fields at the cellular level have current densities equivalent to those induced by a 60 Hz magnetic field of 6.5 G.

5. The earth's magnetic field, which has zero frequency, unless one is accelerating through the field, i.e. flying in an airplane. The strength of the earth's field is approximately 450 mG.
Is EMF Exposure Causally Associated with the Occurrence of Leukemia?

Before answering this question, the mechanism of action must be hypothesized in order to determine whether the effect is stochastic or deterministic.
Is EMF Exposure Causally Associated with the Occurrence of Leukemia?

Before answering this question, the mechanism of action must be hypothesized in order to determine whether the effect is stochastic or deterministic.
Sensitivity of children to the oncogenic effects of ionizing radiation.

Added to this concern is a publication (2002) and statement made at a recent NCRP meeting by Eric Hall, one of the co-authors of the Brenner paper that children are 10 to 15 times more sensitive to the oncogenic effects of radiation than adults.

“It is clear that children are 10 times more sensitive than adults to the induction of cancer” (Hall, 2002).
Attributable Life-time Cancer Risk, % per Sv


Age at time of exposure

Attributable Life-time Risk % per Sv

0 %

5 %

10 %

15 %

Population averages

Female

Male

Nemours Foundation

“The most scientifically credible approach to risk extrapolation to this dose range is a linear extrapolation from greater doses, which is the assumption adopted here.” (Brenner et al, 2001)

“The curvature of the fitted linear quadratic model (for leukemia) is such that the excess risk per unit dose at 1 Sv is about three times that at 0.1 Sv.”

“There is a slightly negative estimated excess risk for the 0.05-0.10 (Sv) category which is not statistically significant.”

“In contrast to solid cancers, all analyses will use a linear-quadratic model for the dose response.” (Pierce et al (1996)

The risk of cancer in children when compared to the risk in adults has confidence limits of <1.0 to 1.8>.
Cancer Epidemiology: According to the National Cancer Institute

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Hypothetical Cancer Risks from CT scans in Children
(Brenner et al 2001)

Life-long cancer risk of 600,000 children 108,000 cancers

500 additional cases of cancer 0.46%

One in every 200 cancers in individuals who had a CT study as a child could be causally related to the CT study exposure.
Between 1990 and 1992 a group of scientists were appointed by the United States Government (Oak Ridge Associated Universities (ORAU)) to undertake a review of the scientific literature dealing with EMF effects related to cancer, behavior, and reproductive effects. Eleven scientists, representing electrical engineering, physics, statistics, epidemiology, molecular biology, cell biology, psychology, teratology, and embryology were appointed to the committee.

Over 2000 research papers and reviews were analyzed and summarized. A final report was published in June 1992 (Davis et al 1992).
Magnetic Fields

There are two sources of low frequency magnetic fields that impact on living organisms over which we have no control.

1. The earth's magnetic field which has zero frequency, unless one is accelerating through the field, i.e. flying in an airplane. The strength of the earth's field is approximately 450 mG.

2. Natural and unavoidable Thermal Electric Fields at the cellular level have current densities equivalent to those induced by a 60 Hz magnetic field of 6.5 G.
Magnetic Fields

A magnetic field equal to $B = 650 \text{ G (60 Hz)}$ acting over the largest diameter loop of tissue (say 40 cm.) in the body will induce current densities ($1 \text{ A/M squared}$), large enough to stimulate cells. Such field levels are usually found in the worst-case industrial or laboratory situations.

$$1 \text{ T (Tesla)} = 10,000 \text{ G (Gauss)}$$
What is the risk of childhood leukemia following embryonic radiation?
Numerous epidemiological studies have been performed. Positive associations for an increased incidence of cancer following in utero diagnostic radiation exposures have been derived almost exclusively from case control studies, while almost all the cohort studies do not find an association.

It is of great interest that the in utero A-bomb population did not demonstrate an increase in leukemia in spite of the fact that many in the in-utero population were exposed to high doses of acute irradiation.
The Risk of Cancer from In-utero Irradiation
(Publications)

# Malignancy Following Preconception Or In-utero Radiation Exposure

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Exposure</th>
<th>Radiation</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart ‘56</td>
<td>In-utero</td>
<td>Diagnostic</td>
<td>44-92%</td>
</tr>
<tr>
<td>McMahon ‘62</td>
<td>In-utero</td>
<td>Diagnostic</td>
<td>50%</td>
</tr>
<tr>
<td>Graham ‘66</td>
<td>Gonadal</td>
<td>Diagnostic</td>
<td>30-100%</td>
</tr>
<tr>
<td>Hoshino ‘65</td>
<td>Gonadal</td>
<td>Atomic bomb</td>
<td>None</td>
</tr>
<tr>
<td>Wood ‘67</td>
<td>In-utero</td>
<td>Atomic bomb</td>
<td>None</td>
</tr>
</tbody>
</table>
The Risk of Cancer from in-utero Irradiation
(Difficulty in Determining the Risk)

“It seems likely that the question of the association between fetal irradiation and childhood cancer will fade into medical history, unresolved and remain a source of more confusion than enlightenment”. (McMahon and Hutchinson 1964)
The Risk of Cancer from In-utero Irradiation

“Learned debate continues as to the causal nature of low level intrauterine radiation and subsequent cancer risks.

The association is not questioned, but the etiological significance is.

Different scientists interpreting the same data have different opinions as to the causal nature of the association and the possible level of risks.” (Boice and Miller 1999).
The Risk of Cancer from In-utero Irradiation

“The risk estimate associated with intrauterine radiation is not substantially greater than that seen following childhood irradiation.” (Muirhead and Kneale 1989, and Mole 1990).

“Irradiation of the fetus in utero increases the risk of childhood cancers, --- an increase in risks is produced by doses of the order of 10 mGy, and thus in these circumstances the excess risk is approximately 6% per Gy “(Doll and Wakeford 1997).
The Risk of Cancer from In-utero Irradiation: A Recent Publication

Naumburg et al, Intrauterine Exposure to Diagnostic X Rays and Risk of Childhood Leukemia Subtypes, Radiation Res. 156, 718-723, 2001,

Case control study of 652 childhood leukemia patients exposed to diagnostic X-rays during various stages of pregnancy compared to matched controls. The ORs were 1.11 (0.83-1.47) for lymphatic leukemia and 1.04 (0.77-1.40) for myeloid leukemia.
A-bomb Survivors Exposed in-utero: Number of Cancer Deaths by Age 46, at Risk, and Cancer Risk by Dose Category

<table>
<thead>
<tr>
<th>Dose (Sv)</th>
<th>Cancer</th>
<th>At Risk</th>
<th>Cancer Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>+3</td>
<td>69</td>
<td>1 in 23</td>
</tr>
<tr>
<td>0.10-0.49</td>
<td>1</td>
<td>215</td>
<td>1 in 215</td>
</tr>
<tr>
<td>0.005-0.09</td>
<td>4</td>
<td>1493</td>
<td>1 in 373</td>
</tr>
</tbody>
</table>

Excludes 2 cancers not known to be induced by A-bomb exposure, pancreas (dose = 1.08 Sv) and uterus (dose = 2.94 meters from hypocenter). Numerator from Miller and Boice (1997, denominator from Otake et al. 1996)
Numerous epidemiological studies have been performed. Positive associations for an increased incidence of cancer following in-utero diagnostic radiation exposures have been derived almost exclusively from case control studies, while almost all the cohort studies do not find an association.

It is of great interest that the in-utero A-bomb population did not demonstrate an increase in leukemia in spite of the fact that many in the in utero population were exposed to high doses of acute irradiation.
The Risk of Cancer from in-utero Irradiation

There is little disagreement with the concept that low doses of radiation present a carcinogenic risk to the embryo and adult and that there may be different risks per rad at different stages of development.

The concept that is difficult to explain from a basic science viewpoint is, “Why would embryonic cells be several orders of magnitude more sensitive to radiation induced cancer than cells of children or adults?” (Brent 1997)
RISK OF DEVELOPING LEUKEMIA
FOLLOWING IRRADIATION

RISK OF LEUKEMIA PER $10^6$ INDIVIDUALS FOLLOWING IRRADIATION

- Stewart et al.
- Animal Data
- A.B.C.C. Data

AGE IN YEARS

EMBryo  FETUS  TERM

RISK OF LEUKEMIA PER $10^6$ INDIVIDUALS FOLLOWING IRRADIATION

100

10

1

1
Counseling Patients with Radiation Exposure with Regard to the Risk of Leukemia

The risk of leukemia is the most difficult to deal with, since radiation induced leukemia is a proven entity and theoretically it is believed to be a stochastic or non-threshold phenomenon.
<table>
<thead>
<tr>
<th>Group</th>
<th>Risk</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical Twin of a leukemic twin</td>
<td>1:5</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>Radiation induced polycythemia</td>
<td>1:6</td>
<td>10 to 15 years</td>
</tr>
<tr>
<td>Bloom’s Syndrome</td>
<td>1:8</td>
<td>&lt; 10 years of age</td>
</tr>
<tr>
<td>Hiroshima survivors &lt; 1000 m hypocenter</td>
<td>1:60</td>
<td>3 to 12 years</td>
</tr>
<tr>
<td>Downs Syndrome</td>
<td>1:95</td>
<td>weeks to months</td>
</tr>
<tr>
<td>Radiation Rx of ankylosing spondylitis</td>
<td>1:270</td>
<td>15 years</td>
</tr>
<tr>
<td>Siblings of a leukemic child</td>
<td>1:720</td>
<td>10 years</td>
</tr>
<tr>
<td>Inutero diagnostic radiation</td>
<td>&lt;1/100000</td>
<td>10 years</td>
</tr>
<tr>
<td>Inutero diagnostic radiation</td>
<td>1:2000</td>
<td>10 years</td>
</tr>
<tr>
<td>U.S. Caucasian &lt; 15 years of age</td>
<td>1:3000</td>
<td>10 years</td>
</tr>
</tbody>
</table>