Assessing the Effectiveness of Risk/Benefit Algorithms:
Radon and Inhaled Particles, for Example

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Some General Points

• Long history of using QRA for environmental agents

• Use of QRA set out in various federal acts and in regulatory processes

• General approaches “codified” through NRC, EPA, and other agencies
Typical Questions

• Is there a risk?
• How does risk vary in relation to exposure (dose)?
• Who is susceptible?
• Who is exposed
• What is the magnitude of the problem?
• What are the benefits of control?
• What is the risk/benefit ratio? The cost/benefit ratio?
The “Red Book”

Elements of QRA

Hazard ID
Dose-response
Exposure assessment
Risk characterization
Evidence Needs for QRA

- Multi disciplinary research in support of causality
- Information on exposure (dose) response and effect modification (susceptibility)
- Information on the exposure distribution
Sources of Evidence

- Hazard Identification: toxicology and epidemiology
- Dose-Response: toxicology and epidemiology
- Exposure Assessment: modeling and population studies
- Many QRAs are done without human data
Indoor Radon and Lung Cancer: Colorless, Odorless Killer?

- Radon ubiquitous indoors
- Concentration log normal
- Some homes have levels as high as mines
- Majority of time spent at home
Four Components of Risk Assessment

• Hazard Identification
  Epi/animal/experiments

• Dose Response
  Epi studies: mines/homes

• Exposure Assessment
  Radon surveys

• Risk Characterization
  BEIR IV and VI approaches
From Exposure To Dose To Risk

Figure 1-2 Factors influencing the relationship between radon exposure and the risk of lung cancer.
• Biological evidence on dose-response
• Analysis of miner data to develop risk model
• Assume linear, no-threshold model
• Exposure from NRRS
• Estimation of attributable risk from radon exposure
Epidemiological Studies of Underground Miners

Uranium Mine: Ambrosia Lake, NM, 1980
Hazard Identification: Epidemiologic Studies

**TABLE 1.**

<table>
<thead>
<tr>
<th>SUBSTANCE MINED</th>
<th>LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uranium</td>
<td>U.S. Colorado Plateau</td>
</tr>
<tr>
<td>Uranium</td>
<td>New Mexico</td>
</tr>
<tr>
<td>Uranium</td>
<td>Czechoslovakia</td>
</tr>
<tr>
<td>Uranium</td>
<td>Ontario, Canada</td>
</tr>
<tr>
<td>Uranium</td>
<td>Beaverlodge, Canada</td>
</tr>
<tr>
<td>Uranium</td>
<td>Port Radium, Canada</td>
</tr>
<tr>
<td>Uranium</td>
<td>France</td>
</tr>
<tr>
<td>Iron</td>
<td>Kiruna, Sweden</td>
</tr>
<tr>
<td>Iron</td>
<td>Grangesberg, Sweden</td>
</tr>
<tr>
<td>Iron</td>
<td>Malmberget, Sweden</td>
</tr>
<tr>
<td>Iron</td>
<td>Northern Sweden</td>
</tr>
<tr>
<td>Iron</td>
<td>England</td>
</tr>
<tr>
<td>Iron</td>
<td>France</td>
</tr>
<tr>
<td>Magnetite</td>
<td>Norway</td>
</tr>
<tr>
<td>Fluorspar</td>
<td>Newfoundland, Canada</td>
</tr>
<tr>
<td>Metal ores</td>
<td>United States</td>
</tr>
<tr>
<td>Zinc-lead</td>
<td>Halmar, Sweden</td>
</tr>
<tr>
<td>Tin</td>
<td>Cornwall, England</td>
</tr>
<tr>
<td>Tin</td>
<td>Yunnan, China</td>
</tr>
<tr>
<td>Niobium</td>
<td>Norway</td>
</tr>
</tbody>
</table>


As radon "passes" the hazard identification step we move on to exposure, dose-response and risk characterization.
Mutagenic effects of a single and an exact number of $\alpha$ particles in mammalian cells

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ABSTRACT One of the main uncertainties in risk estimation for environmental radon exposure using lung cancer data from underground miners is the extrapolation from high- to low-dose exposure where multiple traversal is extremely rare. The biological effects of a single $\alpha$ particle are currently unknown. Using the recently available microbeam source at the Radiological Research Accelerator Facility at Columbia University, we examined the frequencies and molecular spectrum of $S1^-$ mutants induced in human–hamster hybrid ($\text{A}_{1}$) cells by either a single or an exact number of $\alpha$ particles. Exponentially growing cells were stained briefly with a nontoxic concentration of Hoechst dye for image analysis, and the location of individual cells was computer-monitored. The nucleus of each cell was irradiated with either 1, 2, 4, or 8 $\alpha$ particles at a linear energy transfer of 90 keV/μm consistent with the energy spectrum of domestic radon exposure. Although single-particle traversal was only slightly cytotoxic to $\text{A}_{1}$ cells (survival fraction = 0.82), it was highly mutagenic, and the induced mutant fraction averaged 110 mutants per $10^5$ survivors. In addition, both toxicity and mutant induction were dose-dependent. Multiplex PCR analysis of mutant DNA showed that the proportion of mutants with multilocus deletions increased with the number of particle traversals. These data provide direct evidence that a single $\alpha$ particle traversing a nucleus will have a high probability of resulting in a mutation and highlight the need for radiation protection at low doses.
Dose-Response:
Pooled Analysis of Miner Cohorts
BEIR VI: Basis For A Linear Model

In summary, the weight of evidence from cellular and molecular studies strongly supports the concept of linearity with dose in cellular systems including cell lethality, mutation, or transformation with no threshold for low-dose alpha-particle irradiation but leaves open the possibility of a change in slope or a departure from linearity for cancer induction at higher doses. The overwhelming evidence for the monoclonal origin of most cancers suggests linearity without threshold would also apply to low-dose radon-induced carcinogenesis. This observation emphasizes the desirability of extrapolating to typical indoor exposures from the lowest exposure range that is practical in the miner data set.
Exposure Response:
NM and CO Miner Data

Exposure-Response from New Mexico Miners

Exposure-Response from Colorado Miners
Estimates of excess relative risk of lung cancer per WLM and 95% confidence limits for each cohort and for all data combined. Data taken from Table 5. Dotted lines show 95% CI for the combined ERR/WLM estimate based on random effects model.
Exposure-Response

Exposure-Response from Pooled Analysis of 11 Miner Cohorts

All data combined (WLM < 400)

\[ RR = 1 + 0.0049 \times \text{WLM} \]

\[ RR = 1.0 \]
Modeling Exposure Response

TSE/AGE/WL-cat model:

\[ RR = 1 + \beta \times (w_{5.11} + \theta_2 w_{15.21} + \theta_3 w_{25.21}) \times \phi_{ax} \times \gamma_{wl}. \]

where \( \beta = 0.0611, \theta_2 = 0.81, \theta_3 = 0.40, \)

\[ \phi_{ax} = \begin{cases} 
1.00 & \text{for age < 55} \\
0.65 & \text{for 55 \leq age < 65} \\
0.38 & \text{for 65 \leq age < 75} \\
0.22 & \text{for 75 \leq age} 
\end{cases} \]

\[ \gamma_{wl} = \begin{cases} 
1.00 & \text{for WL < 0.5} \\
0.51 & \text{for 0.5 \leq WL < 1.0} \\
0.32 & \text{for 1.0 \leq WL < 3.0} \\
0.27 & \text{for 3.0 \leq WL < 5.0} \\
0.13 & \text{for 5.0 \leq WL < 15.0} \\
0.10 & \text{for 15.0 \leq WL} 
\end{cases} \]
Indoor Studies: Further Evidence on Dose-Response

![Graph showing relative risk against radon concentration (Bq/m³). The graph includes points and error bars for various studies and a log-linear fit to indoor data with 95% CI.]
Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies


Fig 2  Percentage increase in risk of lung cancer per 100 Bq/m³ increase in measured radon concentration by study, age, sex, smoking and histological type....
Radon Exposure Assessment I
The distribution of concentrations in a sample of U.S. homes

Exposure Assessment
(What is the exposure distribution?)

$^{222}$Rn Concentration (Bq/m$^3$)

- GM = 35 Bq/m$^3$
- GSD = 2.8
- AM = 61 Bq/m$^3$
Risk Characterization

• Estimation of population attributable risk using BEIR VI risk model, NRRS data, 1993 mortality data
• Uncertainty addressed qualitatively and quantitatively
• Probabilistic uncertainty modeling carried out
• Smokers—a susceptible subgroup through synergy
Attributable Lung Cancer Deaths
BEIR VI
Uncertainty distributions for the population attributable risk for males. I. Uncertainty in model parameters. II. Variability in K; variability in radon levels. III. Uncertainty/variability in K; variability in radon levels.
Airborne Particles: Sources Are Everywhere
Chain of Accountability

Regulatory Action

Compliance, effectiveness

Emissions

Atmospheric transport chemical transformation and deposition

Ambient Air Quality

Human time activity in relation to indoor and outdoor air quality

Exposure/Dose

Uptake, deposition, clearance, retention

Human Health

Susceptibility factors; mechanisms of damage and repair, health outcomes
Lessons Learned?

• Need for common understanding of concepts and terminology
• Distinction between research, QRA, and risk management
• Understanding of toxicologic and epidemiologic data needs
• Integration of QRA and cost-benefit analysis into decision making
The Radon Example

• The QRA paradigm can work with human data

• Need for pooling of data for “large N” questions: dose-response and susceptibility

• Grounding in mechanistic understanding useful

• Uncertainties can be characterized
For Pharmaceuticals:

• What are the specific questions to be addressed with regard to benefits and risks of pharmaceuticals?
• Get a framework!
• Use it!
• The “Red Book” offers a useful starting point