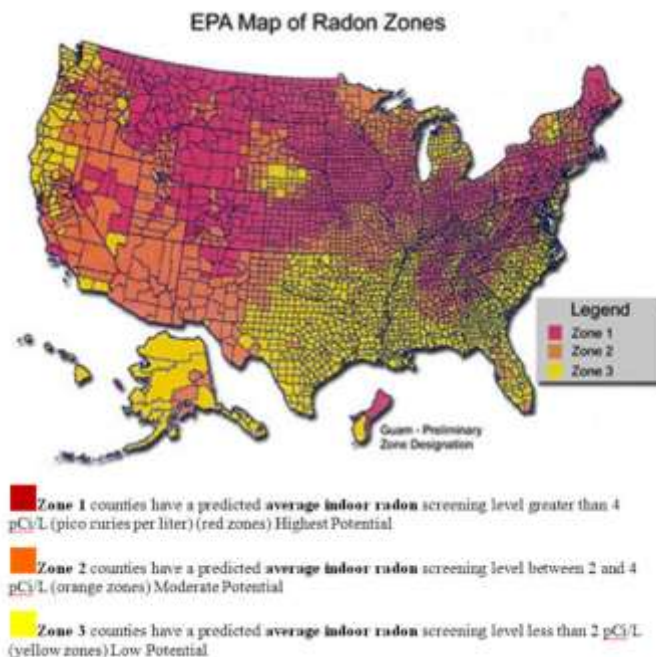


RADON MANAGEMENT PROGRAM

Background

Radon is a radioactive element and noble gas, with the periodic table abbreviation Rn. Radon is found in the rocks and soil of regions where natural deposits of uranium (U) and radium (Ra) exist. The most common isotope of radon is ^{222}Rn , a radioactive element that is a product of the decay chain of ^{238}U . Gaseous radon can migrate through fissures in rocks and soil and seep into basements through cracks in floors or walls, and if these areas do not have significant air movement, radon can build up in basements, crawl spaces, or lower-level building floors.¹ The US Environmental Protection Agency (EPA) publishes county-level data for predicted indoor radon levels based on geology and historical measurements. Fayette County, Kentucky is listed as a Zone 1 county, meaning it has predicted indoor radon activity levels greater than 4 picocuries per liter of air (pCi/L), based on underlying geology.²

Figure 1



As radon gas decays, several radon progeny form. These are short-lived, charged solid particles. Because of their charge, these progeny can adhere to airborne dust particles and deposit deeply into the alveolar regions of the lung. The progeny of greatest concern from a health standpoint are those which emit alpha particles during further nuclear decay, and whose half-life is longer than one second.¹ Once in the lungs, energy generated from nuclear disintegration and emission of ionizing radiation can cause DNA damage in lung cells, and serve as an initiating event for carcinogenic transformation in affected cells.

The University of Kentucky consists of a wide array of buildings utilized for residence halls, classrooms, workplaces, research, and a variety of other purposes. The structural integrity and design of the buildings vary based on construction, maintenance, and location factors. Lower air pressure inside buildings can enable radon to accumulate indoors after diffusing through structural defects such as pores and cracks in the foundation, hollow block walls, and openings around pipes or drains. The permeability of radon into buildings depends on the building construction and surrounding geologic materials. Variation of indoor radon concentrations can be attributed to building type, HVAC systems, floor level, soil conditions, porosity of the bedrock, climate, season of the year, and the nature of the carrier fluids such as carbon dioxide and groundwater.³

Exposure Levels to Trigger Further Actions - Introduction

In order to establish the UK Radon Management Program, one of the first duties was to choose the exposure level (or range of levels) that would trigger additional radon management program elements. Radon gas itself generally does not have an exposure standard, since it is the inhalation and subsequent alpha decay of radon progeny particles that constitutes the primary hazard. Radon exposure guidelines are thus generally measured in terms of activity (disintegration) levels per unit volume of air.

Because a university campus with residence halls has both residential and occupational contexts, standards and recommendations from the U.S. Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) can apply. The historical units for activity levels are picocuries of activity per liter of air (abbreviated pCi/L), where one picocurie equals 2.22 disintegrations per minute.⁴

The EPA does not have an enforceable limit for indoor radon exposures, but issues guidance documents that recommend an indoor residential action level of 4 pCi/L.⁵ Risk calculations are based on an annual average radon concentration for eighteen hours per day, seven days per week for seventy years in a lifetime. When residential structures are tested for radon, the EPA action level is generally used as a point of comparison. Thus, this number is widely considered by the public to be an “exposure limit”.

According to the EPA, the average radon activity level for indoor air concentration in American homes is estimated at 1.3 pCi/L, while radon activity concentrations for

outdoor air average 0.4 pCi/L.⁵ However, this is not by itself an appropriate standard to use at a public university, which consists of occupational, educational, and residential environments that are generally only short-term, and with limited mitigation resources. The rationale for consideration of other trigger exposure levels will be detailed below.

Exposure Levels to Trigger Further Actions – Literature Review

In 1998, the EPA commissioned the National Research Council's sixth Committee on Biological Effects of Ionizing Radiation (BEIR VI) to evaluate all available epidemiological evidence of indoor radon exposures. Many of the studies examined risks in underground miners and indicated an elevated risk of lung cancer, which was also seen in animal studies and other mechanistic data.⁶ A meta-analysis was the basis for many of the Committee's recommendations, and included data from eleven cohort studies of underground miners in seven different countries, pooled together for a total of 65,000 miners and more than 2700 lung cancer deaths.^{6,7} Regression modeling showed a statistically-significant relative risk increase with increasing radon exposures. The authors extrapolated down from the miners' exposures using Linear No-Threshold (LNT) modeling and concluded that residential radon could be responsible for 15,000 lung cancer deaths per year in the U.S., and that compliance with the EPA action level of 4 pCi/L might reduce lung cancer deaths by 2-4%.⁷ However, exposure levels in underground mines are much greater than those found in a residential or office setting.

Based on this available evidence, and adopting the LNT model for extrapolating cancer risks downward from exposure levels in mines to those found in houses, BEIR VI concluded that indoor radon exposure was the second-leading cause of lung cancer in the United States after cigarette smoking, with an estimated rate range of 3,000 to 30,000 deaths per year.⁶ Subsequent analysis cited the LNT model as the most appropriate methodology for extrapolating to very low-dose radiation exposures.⁸

Based on the BEIR VI report, the EPA began a campaign to encourage remediation of buildings if activity levels exceeded the residential "action level" of 4 pCi/L, consider remediation when radon levels ranged between 2 pCi/L and 4 pCi/L, and support of home and school testing for radon.⁹ The EPA's indoor radon emphasis resulted in a growing industry of radon inspectors, abatement system installers, and home testing kits, and spread concern in the population. The Radon Event Planning Kits distributed by the EPA refer to radon as a "silent killer."¹⁰

Some case-control studies that measured actual radon concentrations in residences provided support for the LNT model and EPA action level. One population-based case-control study found elevated lung cancer odds ranging from 0.49 to 0.83 in 1027 female subjects in the state of Iowa, with odds depending on whether categorical or continuous radon exposure measurements were used, and whether all subjects or only living subjects were used.¹¹ Another meta-analysis of seven case-control studies supported the existence of a generally linear dose-response relationship between radon and lung cancer at residential exposure levels.¹² This study pooled data from 4081 cases and

5281 controls, and found an excess odds ratio of 0.10 (-0.01, 0.26) per Bq/m³.¹² However, the separate pooled studies had differing methodologies for radon dosimetry, and different residential mobility inclusion/exclusion criteria that might have resulted in misclassification.

There is also epidemiological evidence against the presence of negative health effects at typical residential radon exposure levels, and other researchers reject the LNT hypothesis outright.¹³ Some studies even point to a possible hormetic relationship between radon and lung cancer. Radiation hormesis theory states that low-level exposures to ionizing radiation stimulate cellular repair mechanisms that can actually reduce the risk of lung cancer or other negative outcomes.¹⁴ Hormesis is a radical paradigm shift from the traditional belief in low-dose linearity for estimating cancer risks, and suggests there could be thresholds for carcinogens.¹⁵

One large ecological study analyzed lung cancer mortality rates versus the average residential radon concentrations in 1601 U.S. counties (representing almost 90% of the U.S. population).¹⁶ This study found a strong and highly significant inverse relationship between average county-level radon exposures and lung cancer rates in the studied range (0 to 7 pCi/L county averages). The strongly negative slope factors were in the opposite direction of values that would be predicted by LNT theory and more than 20 standard deviations distant.¹⁶ While this study had the design weakness of lacking individual-level data, its sheer number of data points and socioeconomic variables make it difficult to dismiss the outcomes as mere ecological fallacy, though it is possible that residential mobility might have confounded the results.¹⁴ A matched case-control study in Massachusetts revealed a profound inverse relationship in the regions with dose rates below 250 Bq/m³ (6.75 pCi/L), and thus an apparent protective or hormetic effect that could not be explained by any known confounder.¹⁷

Radon hormesis is a controversial topic because of its defiance of the traditional, long-accepted LNT paradigm, and anecdotal evidence of beneficial effects from radiotherapy by deliberate exposures in radon spas and other alternative medicines uses of radon are frequently dismissed by Western scientists.¹⁸ More difficult to dismiss are epidemiological studies of nuclear industry workers that demonstrate a hormetic effect between ionizing radiation exposures and all cancers (including lung) that cannot be explained by the healthy worker effect.¹⁹⁻²¹

Overall, the epidemiological uncertainty about the existence of a radon hormetic effect, or the levels at which hormesis ends and harmful effects begin, mean that radon policies should not be enacted based on hormesis theory. However, the epidemiological evidence also does not uniformly support the LNT theory on which the EPA Residential Radon Action Level is based. Therefore, other current standards for exposure to radon progeny or other forms of ionizing radiation were evaluated in order to determine appropriate action levels for campus facilities.

Exposure Levels to Trigger Further Actions – Conclusions

The present Occupational Safety and Health Administration (OSHA) standard for occupational exposures to all ionizing radiation, not just radon progeny, is a time-weighted average of no more than 100 pCi/L per 40-hours in any work week of seven consecutive days.²² This is a legally enforceable standard for all workplaces covered by OSHA, but is based upon a 1971 version of 10 CFR Part 20, the US Nuclear Regulatory Commission Standards for Protection Against Radiation.²³ Because this standard has not been adjusted in subsequent years, and was promulgated strictly for occupational settings, it was not considered an appropriate level for acceptable exposures at the University of Kentucky.

The American Conference of Governmental Industrial Hygienists (ACGIH) is, despite the name, a non-governmental organization that investigates, recommends, and promulgates exposure limits for chemical substances, physical agents, and other workplace stressors.²⁴ These recommended occupational exposure limits, known as the Threshold Limit Values (TLVs)®, have been reviewed and promulgated annually since 1946 and are based on careful study and independent judgment.²⁴ The ACGIH has set an occupational TLV® for radon daughters (progeny particles) which is based on the 2007 recommendations of the International Commission on Radiation Protection in order to keep exposures as low as reasonably achievable while taking economic and societal factors into account.²⁵⁻²⁶ The TLV® for radon daughters is 4 Working Level Months/year (WLM/year).²⁵ In order to make meaningful comparisons, this level was adjusted into units of pCi/L through the steps outlined in Table 1 below.²⁷

Table 1.

Conversion of Threshold Limit Values® from units of Working Level Months to picoCuries per Liter (pCi/L)

| |
|--|
| One working level month (WLM) = one working level (WL) of exposure for 170 hours |
| One working level (WL) = the equivalent of 130,000 mega-electronvolts (MeV) of potential alpha-energy. This is approximately equal to 100 pCi/L of radon at equilibrium with its decay progeny. |
| 4 WLM = 1 WL for 170x4 hours = 680 hours, thus ACGIH TLV = 1 WL for 680 hours |
| American work-week estimate is 2080 hours/year: 40 hour/week x 52 weeks |
| TLV for normal working year = 680/2080 = 0.327 WL |
| 0.327 WL x 100 pCi/L = 32.7 pCi/L* |

*Note that this conversion assumes perfect equilibrium, which is never the case indoors due to ventilation and plate-out.

A common Equilibrium Ratio used for indoor environments is 0.5, which leads to a concentration of 65.4 pCi/L (32.7/0.5) when applied. However, in order to make the most conservative and protective assumptions, perfect equilibrium will be assumed and the lower calculated limit will be used for comparisons.

Ultimately, a tiered approach was utilized for determining actions to take after sampling buildings (Table 2). Because of its basis in sound science, the TLV® adjusted into units of pCi/L, and with conservative assumptions about equilibrium, was chosen as the standard for mitigation.

For on-campus facilities with occupied areas whose measured exposures are above 32.7 pCi/L, mitigation systems are recommended for installation, and these areas are monitored at least quarterly to ensure systems are working as intended. For any space with tested levels between 4 pCi/L (the EPA Residential Radon Action Level) and 32.7 pCi/L, quarterly re-testing is performed, and consideration is given for the feasibility of ventilation controls such as building pressurization or other remediation steps. For spaces with tested levels below 4 pCi/L, no additional action is required, though re-sampling is performed infrequently to ensure that levels remain low during colder weather conditions and as the buildings age.

Table 2. Decision Logic for Buildings Based on Measured Activity Levels

| <u>Activity Levels</u> <u>(pCi/L)</u> | <u>Required Action</u> |
|--|---|
| $x < 4$ | No immediate action required; intermittent retesting |
| $4 \leq x \leq 32.7$ | Re-test at least quarterly; consider ventilation or other controls |
| $32.7 < x$ | Install a mitigation system; monitor performance at least quarterly |

Sampling Methods

Common methods of measurement for radon in buildings include alpha-track canisters, charcoal canisters, working-level meters, and electret ion chamber detectors. Testing can be performed either for short-term (<90 days) or long-term, depending on the method and device.

For the University of Kentucky, passive and reusable short-term electret ion chamber samplers were acquired and deployed. E-PERM® electrets are used for collecting radon measurements and deployed for a minimum of forty-eight hours in each selected location. Electret ion chamber samplers measure the voltage reduction of the positively charged electrets proportional to radon concentrations for duration of 2-7 days of exposures.²⁸ Electret ion chambers require an electronic reader, but do not require separate laboratory analysis and are also the current preferred method by OSHA for measuring radon in workplace atmospheres.²⁹

For sampling, the first priority is to test buildings that have frequently occupied subterranean levels (e.g. finished basements or sub-basements). The age of buildings must also be considered, as older buildings might be more likely to have foundation or wall cracks which allow seepage of radon gas from underlying soils into the building envelope.

Radon activity levels are measured with E-PERM® electret ion chamber samplers, placed and operated in accordance with OSHA Method ID-208.²⁹ Samplers contain two parallel electrets inside a vented plastic case secured with nylon cable ties and tamper-indicating tape (Figure 2). Measurement of radon concentrations in buildings can be subject to sources of uncertainty such as detector measurement error, fluctuation in radon levels with climatic changes, and variances from detector placement.³⁰ Adherence to the testing methods and protocol help control for uncertainty factors; however, short term test results may not be indicative of yearly radon levels contingent on seasonal climatic changes.

Figure 2:
E-PERM® Electret Ion Chamber Sampling Device

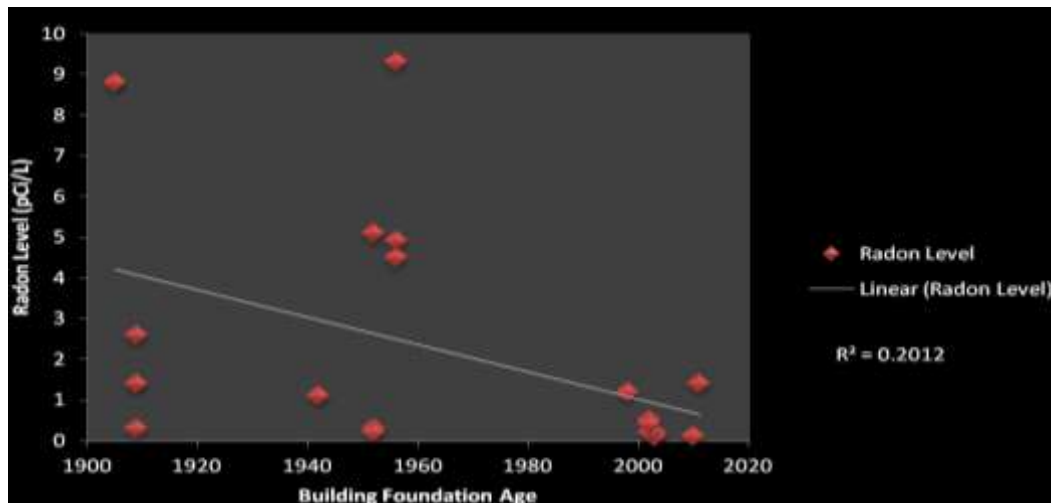


Trends from Sampling Results

Data collected in UK buildings during the Fall 2011 semester was used to determine not only radon activity levels in buildings, but also whether specific building characteristics such as building age, building condition, and campus region were predictors of radon activity level.

Figure 3 shows the linear regression analysis of measured radon activity levels by age of the building. The slope of the linear regression line shows a downward trend of activity levels as building age decreases. The R^2 coefficient of determination value of 0.2012 shows a weak linear relationship caused by large variation in the radon levels among buildings constructed before 1960. The analysis shows that older buildings tended to have higher radon levels. None of the tested buildings constructed after 1960 had levels exceeding 1.4 pCi/L, while five of eleven samples from buildings built before 1960 revealed levels in excess of 4 pCi/L.

Figure 3:
Linear Regression Analysis – Radon Activity Level by Building Age



The categorical (chi-squared) analyses of building age, condition, and region by radon activity samples in excess of 2 pCi/L are presented in Table 3.

Table 3:
Categorical Analysis of Building Characteristics and
Radon Activity Levels

| <u>Age</u> | <u># Samples > 2 pCi/L</u> | <u>P*</u> |
|----------------------|-------------------------------|-----------|
| < 1960 | 6/11 | 0.008 |
| ≥ 1960 | 0/9 | |
| <u>Condition</u> | | |
| Fair/Poor | 6/10 | 0.003 |
| Good | 0/10 | |
| <u>Region</u> | | |
| A | 4/7 | 0.196 |
| B | 2/8 | |
| C | 0/4 | |
| D | 0/1 | |

*Chi Square Analysis p-values

The p-value of 0.008 was calculated for the category of building age, which demonstrated a strong statistical difference between buildings built before 1960 and post-1960. The condition of the buildings analysis yielded a p-value of 0.003, also indicating a strong statistical difference between buildings categorized as good versus fair/poor condition. Region of campus showed no statistical difference with a p-value of 0.196, but two regions had no buildings with samples above 2 pCi/L.

The comparison of mean radon activity levels by the variables of building age and condition, and analysis of variance test by building location are shown in Table 4.

Table 4: Means by Building Categories

| | | N | \bar{x} | GM* | GSD* | Max. Conc. | P-Value |
|--------------------|-----------|----------|-----------------------------|------------|-------------|-------------------|----------------|
| All Samples | | 20 | 2.14 | 0.79 | 4.49 | 9.1 | |
| Age | < 1960 | 11 | 3.5 | 1.8 | 4.1 | 9.1 | 0.0044 |
| | ≥1960 | 9 | 0.47 | 0.29 | 2.8 | 1.3 | |
| Condition | Good | 10 | 0.53 | 0.33 | 2.9 | 1.3 | 0.0069 |
| | Fair/Poor | 10 | 3.74 | 1.9 | 4.4 | 9.1 | |
| Location | A | 7 | 3.7 | 1.9 | 4.5 | 9.1 | 0.0218 |
| | B | 8 | 1.9 | 0.9 | 3.5 | 8.6 | |
| | C | 4 | 0.12 | 0.12 | 1.4 | 0.1 | |
| | D | 1 | 1.2 | 1.2 | - | 0 | |

*GM= geometric mean

*GSD= geometric standard deviation

The p-value of 0.0044 for building age indicates a strong statistical difference in mean radon concentrations between buildings built before 1960 and those built on or after 1960. The variable of building condition with a p-value of 0.0069 suggested that structural integrity and maintenance affect the average radon levels of buildings. The analysis of variance (ANOVA) by building location yielded a p-value of 0.0218, showing that buildings in Region A had significantly higher average radon levels than buildings in Region C, but not significantly higher than buildings in Regions B and D. The average radon concentrations in Regions B, C, and D were not significantly different from each other. With no more than eight samples from any region and only one sample from Region D, the study had too few samples to be able to determine differences in radon concentrations by campus region.

The variables age, condition, and location of the buildings were highly correlated with each other such that older buildings tended to be in poorer condition and located on the same part of campus. Therefore, it was difficult to determine which factor was more important in determining radon concentration, though the results clearly indicate that **both building age and building condition were significant predictors of measured indoor radon activity levels.**

Conclusions

Based on monitoring results and literature review, it was determined that a sampling strategy which focuses first on older buildings, and those with troublesome building envelope maintenance histories, is the best use of limited resources. Furthermore, a tiered approach of action levels for radon risk assessment and management is more appropriate than strict reliance the Environmental Protection Agency's stringent residential radon action level of 4 pCi/L, given the epidemiologic uncertainty, shorter exposure windows, and the need to optimize use of limited infrastructural funds (see Table 2).

Any buildings with tested levels exceeding 32.7 pCi/L will most likely require the installation of a mitigation system to decrease radon activity levels. Follow-up testing of buildings with mitigation systems will be conducted at least quarterly to determine if average activity levels decrease. The second tier of the radon action levels strategy includes areas where one or more sample indicates radon activity levels between 4 pCi/L and 32.7 pCi/L. Retesting at least quarterly would be necessary for areas within this second tier, in addition to consideration for ventilation controls.

All campus buildings with average radon activity levels below 4 pCi/L require no regular action other than sporadic resampling, unless changes are made to building structures that involved excavation of the ground under or around the building, or if changes occur in the ventilation systems of the building. Sporadic resampling of these third-tier buildings can help determine whether aging building envelopes or changing seasonal and climatic patterns are affecting building radon activity levels.

When determining which buildings should receive priority for radon sampling, it appears that building age and building condition are significant predictors of higher radon activity levels in subterranean occupied spaces.

Please contact Brent Webber at UK Occupational Health and Safety (859-257-7600) if you have any questions, comments, or concerns about the UK Radon Management Program.

REFERENCES

1. U.S. Department of Health & Human Services, Radiation Event Medical Management. *Dictionary of Radiological Terms*. <http://www.remm.nlm.gov/dictionary.htm>. Updated March 6, 2013. Accessed July 5, 2013.
2. U.S. Environmental Protection Agency. <http://www.epa.gov/radon/zonemap.html>. Updated September 11, 2012. Accessed July 5, 2013.
3. Al-Zoughool M., Krewski D. Health effects of radon: A review of the literature. *Int J Radiation Biology*. 2009;85(1):57-69.
4. Health Physics Society, 2012. <http://hps.org/publicinformation/ate/q6747.html>. Updated January 31, 2012. Accessed July 5, 2013.
5. U.S. Environmental Protection Agency. *Assessment of Risks from Radon in Homes*. Washington, DC: Office of Radiation and Indoor Air, U.S. EPA; 2003.
6. National Research Council. *Committee on the Biological Effects of Ionizing Radiations, Board of Radiation Effects Research, Committee on Life Sciences, National Research Council. In Committee on the Health Risks of Exposure to Radon (BEIR VI). Health effects of exposure to radon*. Washington, DC: National Academy Press; 1999.
7. Lubin JH et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst*. 1995;87(11):817-827.
8. Brenner DJ et al. Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. *Proc Natl Academy Sci* 2003;100(24):13761-13766.
9. U.S. Environmental Protection Agency. Radon. <http://www.epa.gov/radon/>. Updated February 3, 2013. Accessed July 5, 2013.
10. U.S. Environmental Protection Agency. Radon: Test, Fix, Save a Life Event Planning Kit. http://www.epa.gov/radon/pdfs/nram/event_planning_kit.pdf. Updated March 2012. Accessed July 5, 2013.
11. Field RW et al. Residential radon gas exposure and lung cancer: The Iowa radon lung cancer study. *Am J Epidemiol* 2000;151(11):1091-1102.
12. Krewski D et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Env Health, Part A* 2006;69:533-597.

13. Higson DJ. The bell should toll for the linear no-threshold model. *J Radiol Prot* 2004;24:315-319.
14. Holzman D. Hormesis: Fact or Fiction? *J Nuclear Med* 1995;36(12):13N-16N.
15. Calabrese EJ, Baldwin LA. Toxicology rethinks its central belief. *Nature* 2003;421(13 February):691-692.
16. Cohen BL. Test of the linear no-threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys* 1995;68(2):157-174.
17. Thompson RE, Nelson DF, Popkin JH, Popkin Z. Case-control study of lung cancer risk from residential radon exposure in Worcester County, Massachusetts. *Health Phys* 2008;94(3):228-241.
18. Erickson B. Low dose radon as alternative therapy for chronic illness. Presented at WONUC Conference on the Effects of Low Doses of Ionizing Radiation on Health, Versailles, France, June 16-18, 1999.
<http://www.angelfire.com/mo/radioadaptive/barbara.html>. Accessed July 5, 2013.
19. Prekeges JL. Radiation hormesis, or, could all that radiation be good for us? *J Nuclear Med Tech* 2003;31(1):11-17.
20. Cameron JR and Moulder JE. Proposition: Radiation hormesis should be elevated to a position of scientific respectability. *Med Phys* 1998;25:1407–1410.
21. Abbatt JD, Hamilton TR, Weeks JL. Epidemiological studies in three corporations covering the Canadian nuclear fuel cycle. *Biological Effects of Low-Level Radiation*. Vienna, Austria: International Atomic Energy Agency; 1983. pp.351–361.
22. US Department of Labor, Occupational Safety and Health Administration. 29 CFR 1910.1096.
23. US Department of Labor, Occupational Safety and Health Administration. Standard Interpretations.
http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=INTERPRETATIONS&p_id=24496. Updated December 23, 2002. Accessed July 5, 2013.
24. American Conference of Governmental Industrial Hygienists. About ACGIH: History. <http://www.acgih.org/about/history.htm>. Updated April 30, 2013. Accessed July 5, 2013.
25. American Conference of Governmental Industrial Hygienists. *2013 TLVs® and BEIs® Based on the Documentation of the Threshold Limit Values for Chemical*

Substances and Physical Agents & Biological Exposure Indices. Cincinnati, OH: ACGIH Signature Publications; 2013.

26. International Commission on Radiological Protection. The 2007 Recommendations of the International Commission on Radiological Protection. *Annals of the ICRP*, Publication 103; 2007.
27. Canadian Centre for Occupational Health & Safety. Quantities and units of ionizing radiation.
http://www.ccohs.ca/oshanswers/phys_agents/ionizing.html?print/. Modified June 19, 2007. Accessed July 5, 2013.
28. George AC. World history of radon research and measurement from the early 1900's to today. *AIP Conference Proceedings* 2008;1034(1):20-33.
29. US Department of Labor, Occupational Safety and Health Administration, 1993. Method ID-208: Radon in Workplace Atmospheres.
<http://www.osha.gov/dts/sltc/methods/inorganic/id208/id208.pdf>. Accessed July 3, 2013.
30. Turner MC, Krewski D, Chen Y, Pope CA, Gapstur S, Thun MJ. Radon and lung cancer in the American Cancer Society cohort. *Cancer Epidemiology, Biomarkers & Prevention* 2011;20:438-448.