Review

An Alternative Approach for Investigating the Carcinogenicity of Indoor Air Pollution: Pets as Sentinels of Environmental Cancer Risk

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Traditionally, the cancer risks associated with radon, environmental tobacco smoke (ETS), and similar indoor residential exposures have been evaluated through either laboratory experiments in rodents or epidemiology studies in people. Laboratory studies have the advantage of being controlled experiments, but their utility as estimators of human risk is limited by the uncertainties of extrapolating from rodents to people and from high doses to those typically experienced in the home. These experiments also subject animals to noxious exposures, causing suffering that may be considered cruel. Traditional epidemiology studies evaluate human risk directly, at the exposure levels present in residences; however, these studies are limited by their potential for misclassification, biased recall, and uncontrolled confounding. The long time intervals involved between exposure and disease (often 30 years or more) make accurate recall particularly problematic. In this paper we discuss the limitations of these traditional approaches, especially as they relate to residential studies of radon and ETS. The problems associated with the maximum tolerated dose in rodent bioassays and exposure misclassification in traditional epidemiology are particularly examined. A third approach that supplements the traditional approaches and overcomes some of their limitations is suggested. This approach, dubbed pet epidemiology, estimates residential cancer risk by examining the exposure experience of pet dogs with naturally occurring cancers. The history of pet epidemiology is reviewed and its strengths and limitations are examined. *Key words*: animal sentinel, cancer, epidemiology, indoor air, pets, pollution.
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Indoor air pollution is composed of many different agents that come from a variety of sources. These include volatile organic compounds from building materials, combustion products such as environmental tobacco smoke (ETS), radon gas, molds, dusts, fibers, etc. (*1,2*). Concentrations of many of these substances in the indoor environment exceed median outdoor air concentrations by factors of 2–5 (*3*).

Several of these indoor exposures have been implicated as possible or probable human respiratory carcinogens. Chief among these are radon and ETS (*2*). Radon and its decay products have been characterized as the second leading contributor to lung cancer and as the cause of up to 20,000 (or more) lung cancer deaths yearly in the United States (*4,5*). This figure represents an estimated 10% of all lung cancers in the United States (*6*). Lifetime exposure to the average radon concentration in U.S. single-family houses (40 Bq/m^3) could result in an excess lung cancer risk exceeding 1 in 1,000, with higher exposure levels causing a risk in excess of 1 in 100 [1 Bq/m^3 is equal to approximately 0.04 pCi/liter] (*6*).

Similarly, a growing body of evidence implicates ETS as a possible cause of lung cancer in humans (*7–10*). Environmental tobacco smoke contains numerous carcinogens, including benzene, nitrosamines, and benzo(*a*)pyrene (*8,11*). These carcinogens are often in higher concentrations than in mainstream smoke (*11*). Exposure to environmental tobacco smoke is fairly common, with one study reporting that 63% of the nonsmokers surveyed were exposed to some level of ETS (*8,12*). It has been estimated that 20–30% of the lung cancers among nonsmokers in western countries may be due to ETS (*13*).

Two avenues of research, rodent bioassays and human observational epidemiology, have traditionally been used to investigate the carcinogenicity of pollutants; however, both of these investigational techniques have weaknesses that limit their utility. Because of this, a weight-of-evidence approach to carcinogenicity is usually used. The strength of evidence from both the human data and laboratory data are evaluated and used to classify an agent as a proven, probable, or possible human carcinogen; a noncarcinogen; or not classifiable (*14*).

To complement these approaches and overcome some of their limitations, especially relating to the carcinogenicity of indoor air pollution, we present a third investigative approach: pet epidemiology. This approach uses naturally occurring cancers in pet animals as surrogates of human cancer risk. We will present the history of pet epidemiology as it pertains to the study of domestic carcinogens and discuss the strengths and limitations of the approach. Although this line of research could investigate cats, birds, and other household pets, previous pet epidemiology has investigated dogs almost exclusively. Therefore, we will limit our discussion to dogs and focus on the two main suspect indoor respiratory carcinogens, ETS and radon.

Limitations of Rodent Bioassays

Animal bioassays, as currently practiced, are designed to screen qualitatively for the carcinogenicity of a chemical and to provide data for potency slope estimation (*15*). In these experiments, animals from both sexes of two species (usually rats and mice) are dosed repeatedly with the test agent, and a similar number of control animals are either not treated or treated with placebo. After 2 years (an average lifespan for rodents), both the test and control animals are sacrificed and examined for the presence of cancer in any of their organs.

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The test animals are typically assigned to one to two dosage groups, one of which is the maximum tolerated dose (MTD). The National Toxicology Program (NTP) defines the MTD as "the highest dose of the test agent during the chronic study that can be predicted not to alter the animals' longevity from effects other than carcinogenicity" (*16–18*). This high dose is needed to increase the power of the study to detect an effect in a relatively small number of animals. If a lower dosage group is used, it is usually set at one-tenth to one-half the MTD, which is still quite high compared to realistic environmental exposure levels (*15*). Indeed, bioassays typically do not provide much information about the carcinogenicity of chemicals at doses much lower than half the MTD (*15*).

The MTD provides certain advantages when used as part of a long-term rodent bioassay. It is the dose most likely to induce tumors, thereby both increasing the power of the study to detect carcinogenicity and providing information on the types and locations of tumors caused by the test agent. The MTD also provides a consistent basis for comparison across species, strains, and sexes of animals (*15*). Rodent bioassays also appear to be fairly sensitive at detecting human carcinogens. When proven human carcinogens are also adequately tested via rodent bioassays, the bioassay results are generally positive (*19–21*).

A major limitation of rodent bioassays is that while their sensitivity appears high, their specificity (the ability to accurately detect noncarcinogens) is suspect. When probable human noncarcinogens are evaluated, many are still found to be positive via rodent bioassays (*19*). Ames and Gold (*22,23*) point out that approximately 50% of the more than 400 chemicals that have been adequately tested using rodent bioassays have been identified as carcinogens; this is true for man-made and natural chemicals alike. Other investigators suggest that the percentage of rodent carcinogens is even higher (65%) (*24*). However, only a very small fraction (0.1%) of the 60,000 commonly used chemicals have demonstrated definite evidence of carcinogenicity in people (*21,24,25*). Of course, only a small sample of chemicals, biased toward strong carcinogens with fairly measurable exposure patterns, have been adequately evaluated in people. Even so, this discrepancy has led many to wonder if sometimes it is the methodology, not the chemical, that is carcinogenic (*17,22–24,26–28*).

Many researchers have raised concerns about the utility of laboratory animal assays that use doses at or near the MTD (*20,22–23,28–32*). Potency estimates for typical environmental exposure levels are based on extrapolations from these data, even though these high doses are very different from the low exposure levels found in most domestic situations. These extrapolations are dependent upon the model used and are rarely validated.

High doses of chemicals may alter biologic homeostasis, predisposing an animal to cancer. There are several means by which this may occur. Toxic or near-toxic doses damage tissues, causing mitogenesis as new cells proliferate to replace the damaged ones. Mitogenesis may be a dominant factor in chemical carcinogenesis at high doses (near the MTD) because cell division is a critical part of mutagenesis (*23,28,29, 32–35*). Tissue damage also results in inflammation, releasing free radicals and other oxidants that can damage DNA (*36*). These responses are similar to those of tissue subjected to chronic irritation/wounding, which has been shown to cause tumorigenesis (*23,33,34*).

The NTP definition of the MTD permits a whole-animal toxic dose that results in up to a 10% weight loss in the test animals compared with the controls (*16,17*). Even if a whole-animal toxic reaction is not observed, as might occur at lower doses (i.e., one-tenth to one-half the MTD), specific tissues may receive a toxic dose (*18*). Furthermore, the NTP definition is difficult to interpret (*17,18*), and it has been said that, in practice, "some toxic effects may be inevitable" from the MTD (*27*).

The ultimate goal of rodent bioassays is to make determinations about human carcinogenicity, which requires extrapolating from rats and mice to people. For some exposures, this extrapolation appears to be reasonable. Animal-based cancer potency estimates for asbestos, benzene, and ethylene oxide have been shown to be well within the range of human-based estimates (*37*). However, in many cases, the bioassay results fail to show good agreement even between rodent species. Research has shown that rat and mouse studies identify the same chemical carcinogens only about 50–75% of the time. This is relatively poor agreement, considering both the physical similarity of rats to mice (as compared to humans) and the fact that about 50% of all tested chemicals are rodent carcinogens, making chance agreement more likely (*20,38,39*). Furthermore, rat and mouse studies agree only about 35–50% of the time regarding carcinogenicity at specific target organs (*38–40*). In general, this relative lack of agreement between relatively similar rodent species bodes poorly for the probability of agreement between rodents and people (*38,39,41–43*). In fact, one study showed differences between risks predicted by rodent bioassays and those demonstrated by human epidemiologic data that ranged over 10 orders of magnitude (*39,44*).

There are also many physical, metabolic, and physiological differences between rodents and people, especially regarding respiratory anatomy and physiology (*45–47*). Laboratory rodents, unlike people, generally have poorly defined or absent respiratory bronchioles. Also, because of their small body size, rodents have a much larger relative lung volume. Furthermore, people have quite different particle clearance patterns than do laboratory rodents (*45,46*). The canine respiratory system is far more similar to that of man, although dogs are more expensive and difficult to manage in a laboratory setting.

It is difficult to expose laboratory animals to respiratory carcinogens in a manner that replicates human exposure patterns. For example, researchers investigating the carcinogenicity of tobacco smoke frequently exposed dogs to high levels of smoke for 1–2 daily smoking episodes (*48–51*). This pattern is not consistent with the exposures experienced by people who smoke or are exposed to ETS.

Exposing animals to short-term, high-level inhalation exposures in the laboratory has also caused respiratory illnesses and increased mortality that limit the usefulness of the results. Hernandez et al. (*48*) lost several dogs to asphyxiation and noted that frequent near asphyxiation probably accounted for many of the histopathologic changes seen. In another study, 5 of 10 dogs died after only about 1 year of smoke exposure (*49*). Hammond et al. (*51*) found that approximately one-third of their smoking dogs died from lung and/or heart problems within 2.5 years. Similar life-span shortening has limited the power of radon laboratory studies to detect lung tumors in dogs (*52*).

The animal illness and life-span shortening described above highlight a further problem of laboratory animal studies, which has become more of an issue in recent years—the ethics of subjecting test animals to noxious exposures. Radon and tobacco-smoke studies provide numerous instances of suffering among test animals. Rockey and Speer (*49*) noted that dogs are generally not found to be willing smokers and usually resist forced smoking. Early smoking episodes were usually marked by breath-holding, vomiting, conjunctivitis, and hypersalivation. Numerous respiratory problems, including respiratory infections, bronchitis, emphysema, and increased mortality, have also been noted by investigators (*49–52*). These and other instances

of animal suffering have prompted some authors to suggest alternatives to traditional laboratory animal studies (*53,54*).

Limitations of Traditional Epidemiology

Unlike rodent bioassays, which use a randomized experimental design that limits the potential for bias, all epidemiology studies have an inherent potential for bias because of their observational nature. The various types of bias have been discussed in detail in numerous epidemiology texts and review articles (*55–61*). All of these biases fall into three major classes: selection bias, information bias, and confounding.

Selection bias relates to "systematic differences in characteristics between those who are selected for study and those who are not" (*62*). This is always a potential problem in epidemiologic studies because subjects are not randomly allocated to either index (exposed/case) or referent (unexposed/control) groups, as they are in clinical trials.

Information bias refers to errors in classifying subjects as to either exposure or disease. This bias can be differential if misclassification on exposure depends on disease status (or vice versa), or nondifferential if misclassification on exposure is independent of disease status (or vice versa). Differential misclassification can cause spurious results that are either more extreme than reality or toward the no-effect (null) level, depending on the nature of the bias. Nondifferential misclassification is usually considered to predictably bias results toward the null.

Confounding can also cause spurious results in either direction, more extreme or toward the null. This bias can be thought of as guilt (or innocence) by association. It results from the action of a variable (confounder) that is both a predictor of disease (risk/preventive factor) and associated with exposure. Fortunately, if this confounding variable is identified and adequately measured, confounding can be removed during analysis. Unfortunately, given the multitude of possible confounders, this can be difficult in practice.

Epidemiology texts generally contain guidelines on how to limit these biases (*55,59*). Some investigators from the clinical arena have also published papers suggesting remedies for certain of these biases (*63,64*). However, most epidemiologists acknowledge that it is difficult, if not impossible, to remove all threat of bias from an observational study (*65*). Subsequently, it can be assumed that all epidemiology studies contain some uncontrolled bias.

Biases prevalent in studies of radon and ETS. Studies of radon and ETS highlight two biases that are a problem in all epidemiology studies and that are of particular concern when investigating the effect of these indoor exposures: misclassification and confounding. Misclassification is a problem because it is difficult to piece together a complete exposure history for an individual over a lifetime of 70 years or more. Confounding is a concern because many occupational and behavioral exposures are risk factors for cancer in general (and respiratory cancer in particular).

Misclassification. It is very difficult and expensive to develop a full exposure history for radon case–control studies because a person may live in many different homes during his or her lifetime. In fact, less than half of the radon case–control studies listed as ongoing in 1992 included information on radon levels in previous residences (*66*). Of these, a recent Canadian study made a good effort to identify and test all past homes, although the investigators were able to get measurements for only about 67% of the homes occupied during the critical exposure period 5–30 years before the diagnosis. On average, each participant in this study had occupied nine different residences during his or her lifetime (*67*). The long time periods involved also make it difficult for subjects to recall the duration of residence at each home, the time spent away from home (at work, etc.), and subsequent renovation and/or radon mitigation that may have changed radon levels at a previous residence (*68,69*).

Assessing lifetime exposure to ETS is similarly fraught with problems, with the long time periods involved making recall difficult. Many studies have used marriage to a smoker as a measure of exposure to ETS (*7,70–74*); however, individuals may actually be exposed to three to four times more ETS at the workplace (*75*). People are also exposed to ETS in restaurants, while socializing or traveling, and in many other places. The extent of this exposure may be significant, but it is difficult for subjects to recall adequately (*10,75*). Furthermore, estimates that only include adult exposure ignore exposure from parental smoking during childhood. Some studies have suggested that childhood exposure may be important at certain cancer sites or for certain subpopulations (*71,72,76*).

Confounding. Confounding is also a problem when trying to determine the cancer risk from low-level domestic exposures, such as radon and ETS. Cancer can have multiple etiologies, making it difficult to gauge the independent effects of ETS and radon. Lifestyle and dietary factors are estimated to account for the largest proportion of human cancers (*77*). People engage in risky behaviors such as active cigarette smoking, which has been estimated to account for approximately one-third of all human cancer and is the leading cause of lung cancer in the United States (*77*). People may also be exposed to carcinogens in the workplace. It has been estimated that approximately 4% of all cancers are occupationally induced (*77*), although some investigators believe that this figure is much higher (*78*). Occupational exposures to radon, chromium, nickel, arsenic, asbestos, bis(chloromethyl)ether, wood dust, soots and tars, and several other chemicals/agents are considered proven causes of human respiratory cancer (*25,79,80*). Confounding variables may mask the true association between ETS, radon, and cancer.

Confounding can be controlled when it can be adequately measured. However, the long time periods involved and the sparsity of exposure records make it difficult to adequately measure potentially important confounding factors. The resulting misclassification of confounders can be even more problematic than misclassification of exposure. It can usually be assumed that misclassification of exposure is nondifferential, resulting in a predictable error toward the null and only a loss of power. However, misclassification of confounding variables results in residual (uncontrolled) confounding, which can cause a spurious result that is more extreme than expected. For example, some people who classify themselves as nonsmokers may actually be past or low-level smokers. These misclassified people are at somewhat increased cancer risk (from smoking) and are also more likely to marry/associate with other smokers. Therefore, this misclassification introduces confounding into ETS/cancer studies, resulting in a cancer risk that is overestimated (*71*).

Pet Epidemiology

History of pet epidemiology. Domestic animals have functioned as natural sentinels of environmental health hazards since at least the middle ages, when the effects of ergot-contaminated grain were recognized in livestock (*81*). Recognition of the health effects to people of toxic releases has frequently been preceded by epidemics of disease in domestic animals. For example, the death of cattle at a livestock show in England in 1873 was associated with a dense industrial fog (*81*). This occurred well before the human health effects of air pollution were routinely recognized. More recently, polychlorinated biphenyl-contaminated rice oil caused the death of over 400,000 chickens in Japan 6 months before the Yusho rice oil incident that affected over 1,000 people in that same

Table 1. Key studies that utilized pet-animal epidemiology to investigate the environmental causes of cancer

Study Type	Exposure	Association[a]	Disease	Reference
Prevalence comparison	Rural vs. urban	8.8[b] (1.9–40.6)	Tonsilar carcinoma	(83)
Prevalence comparison	Rural vs. urban	7.4[b] (3.2–17.6)	Pulmonary changes	(84)
Crude CC	Rural vs. Urban	3.3[b] (1.5–7.5)	Tonsilar carcinoma	(85)
Mortality correlation	Level of local industry	$r = 0.59$ ($p = 0.03$)	Bladder cancer	(86)
Crude CC	Number of asbestos bodies	$t = 4.08$[b] ($p<0.01$)	Mesothelioma	(87)
CC	Asbestos occupation or hobby	8.0 (1.4–10.6)	Mesothelioma	(88)
CC	Topical insecticide	4.2 (1.4–12.1)	Bladder cancer	(89)
Prevalence comparison	Vietnam service	2.0 (1.2–3.5)	Seminoma	(90)
CC	Herbicide use	1.3 (1.0–1.7)	Lymphoma	(91)
CC	Passive smoke	1.6 (0.7–3.7)	Lung cancer	(92)
CC	Electromagnetic fields	6.8 (1.6–28.5)	Lymphoma	(93)

CC, case–control; OR, odds ratio.
[a]Unless otherwise indicated, the measure of association is the OR. The numbers in parentheses are 95% confidence intervals or *p*-values.
[b]These ORs/tests were not included in the original publications and have been calculated by one of the authors (JAB).

country (*81*). Similarly, the environmental health effects of aflatoxin, chlorinated naphthalene, dioxin, DDE, leptophos, organic mercury, and other chemicals were first identified in domestic animals (*81,82*).

These early animal-sentinel examples dealt primarily with acute intoxications among farm animals. Pets are better suited as sentinels of chronic exposure to residential carcinogens because of the intimate association between pets and the domestic environment of people. However, studies of residential exposures in pets are limited to a relatively few investigations that have been conducted over the last 20–30 years. Most of these have investigated potential domestic carcinogens (Table 1) (*83–93*).

In 1967, Ragland and Gorham (*83*) noted an eight times greater prevalence of tonsillar carcinoma among dogs from an urban area (Philadelphia, PA) compared with dogs from rural Washington State. This urban/rural difference in the prevalence of tonsillar carcinoma was later confirmed by Reif and Cohen (*85*). Reif and Cohen (*84*) also noted that there was a greater prevalence of chronic pulmonary changes in the lungs of older dogs that had lived in urban areas. Similarly, a study performed by Hayes et al. (*86*) showed a significant positive correlation between the proportional mortality ratio (PMR) for canine bladder cancer and level of industrial activity in the host county of the animal hospital.

The early observational studies cited above were somewhat crude in design and suffered from significant deficiencies. Two of these studies were primarily correlational, with limited data regarding exposure or disease among individual dogs (*83,86*). None of the investigators contacted the dog owners to obtain information on exposures or potentially important confounding variables. Exposure measurements were limited to crude estimates of regional industrialization or urbanization, creating the potential for significant misclassification (*83–86*). Potential confounders were limited to age, breed, and sex, although only two of the studies adjusted for these variables in the analysis (*84,86*). Furthermore, all of the investigators were limited analytically because of the lack of modern computerized statistical methods.

During the last two or three decades, refinements to the case–control approach have made this a key epidemiologic tool (*57,94*), and more recent pet cancer epidemiology studies have used the case–control approach. A case–control study by Glickman et al. (*88*) demonstrated a significant positive association between canine mesothelioma and an asbestos-related occupation or hobby in a household member. These findings were supported by those of Harbison and Godleski (*87*), who found significantly more asbestos bodies (asbestos fibers coated with an iron protein complex) among dogs with mesothelioma than among control dogs. These two studies confirmed this common cause for human and canine mesothelioma. They also showed the utility of dogs as markers of asbestos exposure, an idea suggested in 1931 by the diagnosis of asbestosis in a dog that lived in an asbestos factory (*95*).

Several other case–control studies on cancer in pets have been reported. Glickman et al. (*89*) demonstrated an association between topical insecticide use and canine bladder cancer. Hayes et al. (*91*) showed a small but significant association [odds ratio (OR) = 1.3] between canine malignant lymphoma and the application of phenoxy herbicide lawn care products. Reif et al. (*92*) found a weak association [OR = 1.6; 95% confidence interval (CI), 0.7–3.7] between ETS and canine lung cancer. However, this study found that the increased risk was restricted to dogs with short- or medium-length noses, suggesting that nasal cancer may be a better endpoint for this exposure than lung cancer (*92*). Most recently, Reif et al. (*93*) demonstrated an increased risk for lymphoma among dogs exposed to electromagnetic fields around the home.

These case–control studies were methodologically superior to the earlier studies reported. Most of the investigators gathered information on exposure and confounding variables directly from the owners (*88,89,91–93*). Also, the availability of computers, as well as the statistical advances associated with them, allowed for improved analyses. Confounding variables were controlled either through stratification (*88,92*) or through logistic regression modeling (*89,91,93*).

Advantages. Usually, no single study can be used to make the determination that an individual environmental agent causes a particular cancer. Instead, a weight-of-evidence approach is used. In general, well-designed pet epidemiology studies can add significantly to the weight of evidence concerning the environmental causes of cancer in both animals and people. This approach forms an attractive addition to traditional laboratory animal and human observational investigations.

When evaluating causality using a weight-of-evidence approach, similar findings across varied studies is one of the key criteria to consider (*59*). For example, a positive epidemiologic association is more credible if it supports the findings of other epidemiologic studies or of laboratory animal studies. A positive result from a pet epidemiology study would further enhance the credibility of the association. Pet epidemiology

studies could also act as a tie-breaker when the results from traditional approaches are at odds.

The approximately 50 million pet dogs currently in the United States represent a relatively untapped source of information on disease causation. Many of these dogs come from genetically distinct breeds with varying risks for particular cancers, facilitating the differentiation of genetic influences from environmental ones (*54*). Furthermore, the owners of these dogs are often very cooperative, and participation rates for pet epidemiology studies are high. For their study investigating the association between canine malignant lymphoma and herbicide exposure, Hayes et al. (*91*) noted that of the over 1,400 case and control owners contacted, only four refused to participate.

In many respects, pet dogs form an excellent surrogate population for exploring the carcinogenic potential of the domestic environment in which people live. Pet dogs live in close association with people and share domestic exposures with them; however, dogs do not directly engage in the high-risk behaviors and occupations experienced by their human masters. Also, dogs have shorter life spans and cancer latency periods than do people, allowing them to be used as early sentinels of environmental problems. Furthermore, only fairly recent environmental exposures need to be measured, enhancing the quality of recalled information and minimizing both exposure misclassification and recall bias (*54*). Differential recall would still be possible, but it is likely that people would not experience the same recall stimulus from cancer in a pet as they would from their own cancer or that of a close family member.

Active smoking and occupation are the major confounders that plague traditional environmental epidemiology studies. Pets are free of these exposures, although low-level exposure to workplace carcinogens may still occur from materials (e.g., lead and asbestos) that adhere to clothing worn in the workplace. The relatively short recall period in pet studies would enhance the measurement of other less critical confounding factors (such as diet and socioeconomic status), thereby limiting residual confounding from incomplete control of these factors.

Dogs have also been shown to be good models for many human cancers. Several investigators have demonstrated that canine and human mammary cancer share important clinical and histological features (*96–99*). Other authors have shown similarities between human and canine bone cancer (*100,101*), bladder cancer (*86,97,102*), and nasal cancer (*103*). Dogs have been shown to be especially good models for human respiratory cancer and have been used in laboratory studies to investigate the health effects of exposure to both tobacco smoke and radon. Cigarette smoke has been shown to cause similar histologic changes to the lungs of both people and beagle dogs (*50,51*). Radon has been shown to cause lung cancer in laboratory dogs at levels that did not greatly exceed exposures reported for uranium miners (*52*). Dogs are also similar to humans in that their incidence of respiratory tract tumors is linearly related to both increasing cumulative radon exposure and unattached fraction (*52*). In general, the dog is the best model for inhalation studies in which comparisons to humans are to be made (*45*).

Pets are not only good markers of effect; they have also proven to be useful markers of exposure. Thomas et al. (*104*) found that pet dogs with high blood lead levels could be used to predict higher blood lead levels in children from the same family. Kucera (*105*) found a positive correlation between blood lead levels in pet dogs and the density of nearby local traffic patterns, highlighting the historical importance of this route of human exposure. More recently, Reynolds et al. (*106*) found significantly higher urinary levels of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) among dogs from treated homes compared to those from nontreated ones. However, differences in absorption, metabolism, and excretion between dogs and people must always be considered when using pet dogs as exposure sentinels. For example, Reynolds et al. (*106*) found elevated 2,4-D levels in canine urine samples even more than 2 weeks following exposure. People excrete 2,4-D much more rapidly, eliminating almost the entire absorbed dose in approximately 4 days (*107*). Relying solely on canine exposure models would greatly overestimate 2,4-D body burdens in people.

Observational studies of pet populations also represent a humane alternative to laboratory animal experimentation (*54*). Unlike laboratory animal studies, the cases in pet cancer studies are not subject to noxious or debilitating exposures by investigators. Well-designed pet epidemiology studies can provide an additional independent approach to cancer research, thereby reducing the number of laboratory animal studies needed to build a body of evidence for carcinogenicity.

Limitations of pet epidemiology. Pet epidemiology studies are observational in nature and therefore share many of the biases inherent in human epidemiology. Exposures are still usually estimated from retrospective interviews, setting up the possibility of misclassification and recall bias. Similarly, selection bias and confounding are potential problems. However, as mentioned previously, the magnitude of these biases should be greatly lessened in pet studies. Also, the same techniques used to limit these biases in human epidemiology studies (e.g., cancer controls to limit differential recall, stratified or multivariate analyses to control confounding, etc.) can be applied to pet studies as well.

An important limitation of pet epidemiology is a lack of essential population and disease data. Only a handful of U.S. animal disease registries have ever existed (*108–110*). Monsein (*110*) suggests that these suffer from inaccuracies, biases, and an inability to provide reliable incidence or mortality rates, which limits their utility for analytical epidemiology studies. Use of the case–control approach has overcome much of the need for population rates but not the paucity of available disease data. Most of the case–control studies on cancer in pets have contained fewer than 100 cases. Only the malignant lymphoma study reported by Hayes et al. (*91*) had sufficient power to detect relatively small associations. This study contained almost 500 cases and more than 900 tumor and nontumor controls.

This paucity of accurate disease information is (in large part) driven by economic considerations. Although veterinary care has an absolute cost that is much less than similar human medical care, the lack of third-party reimbursement makes veterinary care relatively more expensive and unaffordable to many dog owners (*54*). When faced with a severe chronic disease such as cancer, many owners opt for euthanasia rather than pursuing expensive diagnostics and treatment. These cases are never presented to a veterinary teaching hospital where they might become part of a diagnostic or histopathology database. Because there are also no mandated death or cancer registries for dogs, only a small fraction of cancer cases could be expected to come to the attention of veterinary epidemiologists.

An additional economic consideration that hampers pet cancer epidemiology is the lack of available funding. Agencies that traditionally support similar human cancer epidemiology may not appreciate the potential benefits of a pet approach. Glickman and Domanski (*54*) cite an example of a study investigating diet and canine breast cancer, which was submitted to a major federal funding agency. The reviewers acknowledged the similarities between canine and human breast cancer and the relevance of the research. They also noted that this research would address an important issue that is difficult to assess by observational research in women. However, they gave the study a low priority because "For all its virtues, however, this is a study of

dogs and can never achieve the priority of a comparably designed study in humans" (*54*).

The above opinion reflects a lack of comfort with the pet approach, which may be shared by many researchers. The herbicide/canine malignant lymphoma study by Hayes et al. (*91*) was harshly criticized for relying on questionnaire responses and not ascertaining actual herbicide body burdens (*111,112*). However, a similar level of criticism was not leveled at the large number of human epidemiology studies that have relied on questionnaire responses, nor did the critics consider the advantages of the shorter recall period possible in this pet epidemiology study. These critics were apparently unable to separate the novelty of the approach from its strengths and weaknesses.

Conclusion

For many reasons, pet cancer studies form a valuable complement to laboratory animal and human epidemiology studies. Pets live in intimate association with the local domestic environment of people and represent good models for many types of human cancers. These studies usually obtain good compliance from pet owners, who are often excited about the possibility that the cancer in their pet could help further the war against cancer. Also, the information that these owners supply may be of better quality than that obtained in similar human retrospective studies because pet owners only need to recall a relatively short time span of 5–15 years. Finally, pet cancer studies never subject animals to noxious exposures, thereby representing an attractive alternative to laboratory animal approaches.

Certainly, pet research cannot totally replace the more traditional research techniques; however, pet studies represent a unique line of inquiry that explores cancer causality from an independent direction. This makes pet studies ideally suited to the weight-of-evidence approach that is currently used to define the carcinogenic potential of environmental exposures.

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29TH MEETING OF THE ENVIRONMENTAL MUTAGEN SOCIETY

MARCH 21–26, 1998
DISNEYLAND HOTEL, ANAHEIM CALIFORNIA

DEADLINES:

LATE-BREAKING ABSTRACTS:	JANUARY 23, 1998
ADVANCED REGISTRATION:	JANUARY 23, 1998
DISNEYLAND HOTEL REGISTRATION:	FEBRUARY 20, 1998

SYMPOSIA:

DNA DAMAGE:	
MITOCHONDRIAL DNA	B. VAN HOUTEN
DNA REPAIR:	
TRANSCRIPTION COUPLED REPAIR AND HUMAN DISEASE	P. HANAWALT
INTERACTIONS OF RAD51 AND BRCA1	L. THOMPSON
MECHANISMS OF SPONTANEOUS MUTAGENESIS	T. KUNKEL
GENOMICS:	
ANALYSIS OF GENOMES FROM DROSOPHILA TO MAN	A. CARRANO
RISK ASSESSMENT:	
CASE STUDIES OF CHLOROFORM, BUTADIENE, ASBESTOS, AND PHENOLPHTHALEIN	V. DELLARCO AND D. JACOBSON-KRAM
DOSE RESPONSE AND THRESHOLDS	G. KRISHNA; B. GOLLAPUDI
ENVIRONMENTAL GENOMICS:	
GENE–ENVIRONMENT INTERACTIONS IN HUMAN GENETIC DISEASES	R. ALBERTINI
HUMAN MONITORING AND MOLECULAR EPIDEMIOLOGY OF CANCER	D. ANDERSON; C.AMBROSONE

MINI-MEETING

TRANSGENIC ANIMALS IN MUTAGENICITY/CARCINOGENICITY STUDIES	B. GLICKMAN AND N. GORELICK (1 1/2 DAYS)

WORKSHOPS, STUDENT PROGRAMS, EXCURSIONS, AND DISNEYLAND

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