Non-Linearity Between Dose and Cancer Risk for Internally Deposited Alpha Emitters in Animals

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This work is supported jointly by the Canadian Nuclear Society, the CANDU Owners Group, MDS Nordion, COGEMA Resources Inc., Électricité de France, the US Department of Energy, and the Central Research Institute of the Electric Power Industries (Japan).

Abstract

The risk of cancer in experimental animals exposed to low doses and dose rates of internally deposited alpha emitting radionuclides was analyzed in 27 animal experiments comprising 78 groups exposed to specific dose levels (dose groups). In these experiments, 3041 animals were exposed to eight different alpha emitters, by injection or by inhalation. Radiation doses ranged from about 60 mGy to more than 7 Gy. There were 1655 control animals. The target organs were the lung and the skeleton. The cancer incidence in exposed groups was compared to that predicted by the Linear No-Threshold Hypothesis (LNTH). In the 3041 exposed animals, 49 cancers were observed, against 83 predicted by the LNTHT. The LNTH appears to be a reliable risk predictor in 11 of the 78 dose groups, but it overestimates the risk in the 67 other dose groups (71 predicted cases, 8 cases observed). No cancer was observed in 53 dose groups, when 23 were predicted by the LNTH. In these 53 dose groups, the probability of not observing a single case of cancer was extremely small. These observations led to the conclusion that, at least in the case of alpha emitters with long physical and biological half-lives, the LNTH is not a good predictor of the risk of cancer.

1. Introduction

The literature has been reviewed to identify and collect papers on animals studies which provide quantitative information on the relationship between cancer incidence and absorbed dose in organs, from internally deposited alpha emitting radionuclides with long physical and biological half-lives. The review concentrates on the risk of cancer observed in the lowest dose groups, which also correspond to low dose rates. Since the objective of this work was to test the validity of the LNTH, the analysis of the data was restricted to the effects of doses that did not reduce the life expectancy of the subjects, or for which no cancer was observed in the exposed animals. Nevertheless, the doses and dose rates considered in this review are generally much larger than those received occupationally, currently or historically.

With a few exceptions, the number of animals in control and exposed groups was small, the number of cancer cases was also very small, and frequently equal to zero in the exposed groups

and in the controls. As a consequence, the cancer risk per unit exposure obtained for each exposed group has very large confidence intervals and P values. No conclusion regarding the validity of the LNTH could be drawn from individual exposed groups. However, it was observed that the LNTH predicted more cancer cases than actually observed in 67 of the 78 dose groups This illustrates the need to search for new methods for testing the validity of the LNTH at low doses.

In order to avoid the use of speculative tissue weighting factors in animals, the absorbed dose, *not the effective dose* is used in this paper as a measure of radiation risk.

2. Definitions

Some terms are used in this paper in a specific sense. They are defined below.

Animal experiment: An experiment in which groups of animals of the same strain, age, and origin have been exposed to various dose levels of the same radionuclide.

Dose group: Refers to a group of animals within an animal experiment, which received the same average dose of the same radionuclide.

Predicted Risk Factor: The risk of cancer per unit dose calculated according to the LNTH. At dose D = 0, the linear fitted line intersects the risk axis at the value equals to the spontaneous cancer incidence rate in control animals. The predicted risk factor is expressed as the Odds Ratio per Gy. When the number of cancer cases is small in the control and exposed groups, and when the relative risk is close to unity, the Odds Ratio is a good approximation of the relative risk (Ahlbom 1993).

Odds ratio: The Odds Ratio per unit dose is the measure of risk used in this paper. The Odds ratio is estimated by

$OR = a.d/b.c$

With
a = number of cancer cases in the exposed animals
b = number of cancer cases in the non-exposed animals
c = number of exposed animals
d = number of control animals

3. Material and methods

3.1 Selection of experimental data

There is only a limited number of animal experiments which provide information concerning the induction of cancer induction by internally deposited alpha emitters at low doses and low dose rates. This is because animal studies take a long time to complete and are very expensive.

The studies analyzed in this paper are:

- The study on the effects of inhaled $^{239}PuO_2$ in rats (Sanders 1988 and 1993);
- The study of the effects of ^{226}Ra injected in beagle dogs (White 1994);
- Another study of the effects of ^{226}Ra injected in beagle dogs (Mays 1987);
- The study of the relative biological effectiveness of ^{226}Ra, ^{239}Pu, ^{241}Am, ^{249}Cf, and ^{252}Cf injected to C57BL/Do mice (Taylor 1983).

In the interpretation of animal experiments, it is important to remember that they present some major strengths:

a- the animals are exposed to known quantities of radionuclides, whose chemical and physical forms are well characterized;

b- the dose received by the organs of interest can be established accurately, generally by direct measurements of the amount of radionuclide deposited in the organs;

c- the animals are not exposed to other potential carcinogens, and the observed effects are not confounded by co-carcinogens;

d- the cancers induced by radiation in experimental animals occur rarely in non-exposed animals (for example, bone cancer in beagle dogs, lung cancer in Wistar rats). Therefore, the excess of cancers cases observed in these animals can be safely attributed to radiation exposure.

The experimental data used in this review are given in Table 1.

3.2 Determination of the risk of cancer at each dose level

3.2.1 Theoretical risk per unit dose

From the linear no-threshold theory, the theoretical cancer incidence rate is related to dose by the general expression

$$I_{th} = m + \alpha D \qquad (1)$$

where

I_{th} is the theoretical cancer incidence rate in exposed animals;
m is the cancer incidence rate in control animals;
α is the slope of the dose-effect equation (risk per unit dose); and
D is the dose (in Gy).

For each animal experiment, the OR_{Obs} values were plotted against corresponding dose values

and the points were fitted with equation 1, which determines α, the risk per unit dose. R and α values are given in Table 1. An example of the LNTH dose-effect relationship is given in Figure 1. Graphs such as that in Figure 1 were produced for each animal experiments. The goodness of fit (R) between the best linear fit and the data points was also calculated for each experiment, and R values are given in Table 1.

3.2.2 Theoretical number of cancer cases at each dose point

In each exposed group and for each dose level, the number of cancer cases predicted by the LNTH is given by:

$$x_{th,D} = (m + \alpha D)\, n(D) \qquad (2)$$

where

$x_{th,D}$ is the number of cancer cases predicted by the LNTH in n animals exposed to dose D.

Examples of x_{th} values are given in Table 1.

3.2.3 Methods used to test the Linear No-Threshold Theory

From the observed and predicted numbers of cancer cases in each dose group, two methods were used to test the validity of the LNTH:

1 – The Odds Ratios for the observed and theoretical numbers of cancer cases were calculated by means of 2 x 2 contingency tables, and were compared in three dose group subsets:
   - dose groups in which the observed number of cases was equal or larger than predicted by the LNTH;
   - dose groups in which the observed number of cases was smaller (including zero) than predicted by the LNTH;
   - dose groups in which the observed number of cases was zero;

2 - The probability of observing the number of cases actually observed was determined based on binomial statistics.

4. Results and discussion

4.1 Testing the LNTH by comparing the odds ratios in various groupings of dose groups

As indicated above, the odds ratio for the observed numbers of cancer cases was determined for each dose group. In addition, a theoretical OR value, OR_{th}, was calculated from the theoretical number of cancer cases predicted by the LNTH. OR_{th} is a theoretical measure of the radiation risk based on the linear no-threshold hypothesis. The observed and theoretical odds ratios (OR_{Obs}, OR_{th}) were compared by means of the unconventional use of contingency tables described below, which is a comparison of the observed and predicted numbers of cancer cases.

To that effect, a special odds ratio, called Compatibilty Ratio (CR), was defined as

$CR = ad/bc$

with

a = predicted number of cancer cases in exposed animals
b = predicted number of exposed animals without cancer
c = observed number of cancers cases in exposed animals
d = observed number of exposed animals without cancer

The Compatibility Ratio (CR) is a measure of compatibility between the predictions of the LNTH and the experimental results. CR can be interpreted as follows. The LNTH is deemed to hold if CR is close to one, with a confidence interval, which includes one. Similarly, LNTH is deemed to hold for a given set of animal experiments if the OR_{Obs} and OR_{th} values are close and if their respective confidence intervals overlap. If the above conditions are not met, the LNTH is not a good predictor of the radiation risk under the considered experimental conditions.

4.2 Odds Ratios for different groupings of the results of the animal experiments

The odds ratios were calculated and compared for total observed and predicted numbers of cases for three subsets of data

- one in which the observed number of cases exceeds the number predicted by the LNTH ($x \geq x_{th}$);
- one in which it was smaller ($x \leq x_{th}$);
- and one in which no cancer was observed in the exposed animals ($x = 0$).

The odds ratios were also calculated for the entire set of data. They are given in Table 2.

4.3 Dose groups in which $x \geq x_{th}$

Compared to control groups, the risk of cancer was clearly elevated in the 11 dose groups, in which the observed number of cancer cases was at least equals to the numbers predicted by the LNTH. In this subset, there were 18 cases observed against 14.6 predicted. The observed and predicted numbers of cancer cases were comparable (OR_{Obs} = 12.6, C.I. = 3.0 - 54.0, $P \leq 0.0001$; and OR_{th} = 11.5, C.I. = 2.6 - 51.0, $P \leq 0.0001$) (see Table 3 for details). Furthermore, CR = 1.2 (C.I. = 0.5 - 2.5). For that group of data, experimental data and LNTH prediction were in agreement.

4.3.1 Dose groups in which $t < x_{th}$

There are 67 dose groups in which the number of observed cancer is smaller than predicted by the LNTH (33 versus 70.8) (Table 2). In this subset of dose groups, there were 2887 exposed animals and 1655 controls, with 8 cancer cases in the 1655 controls. In this pool of data, there was still an excess of cancer cases in the exposed animals compared to the controls, but the

number of observed cases was significantly lower than predicted by the LNTH (OR_{Obs} = 2.4, C.I. = 1.1 - 5.1, P = 0.035; OR_{th} = 5.2, C.I. = 2.5 - 11.0, P ≤ 0.0001). The discrepancy between the observed and predicted numbers of cancer cases was confirmed by the value of the compatibility ratio (CR = 0.4, C.I. = 0.24 - 11.0, P ≤ 0.0001). There was some overlap between the OR_{Obs} and ORth confidence intervals, but these results suggest that, for this group of experimental data, the relationship between dose and cancer induction is sublinear.

4.3.2 Dose groups in which x = 0

There are 53 dose groups in which no cancers were observed in the 753 exposed animals, versus 6 in the corresponding 603 controsl (Table 2). In this pool of data, the deficit in cancer cases, relative to the number predicted by the LNTH (22.5), was statistically highly significant (OR_{Obs} = 0.06, C.I. = 0.003 - 0.1, P = 0.008; OR_{th} = 3.2, C.I. = 1.3 - 12.0, P ≤ 0.0001). In these dose groups, there was no overlap between the confidence intervals of OR_{Obs} and OR_{th}. Furthermore, with CR = 0.02 (C.I. = 0.001 - 0.34, P < 0.0001) there seemed to be no doubt that, in 53 out of a total of 78 dose groups, the relationship between dose and cancer induction was sub-linear and possibly included a threshold.

4.3.3 All dose groups

In the 78 dose groups analyzed, 49 cancer cases were observed in 3041 exposed animals, against 83.4 predicted by the LNTH. In 1655 control animals, 8 cancer cases were observed. Owing to the overlap between OR_{Obs} and OR_{th} confidence intervals, the deficit in observed cases was not quite significant (OR_{Obs} = 3.3, C.I. = 1.6 - 7.0, P = 0.001; OR_{th} = 5.8, C.I. = 2.8 - 12.0; P ≤ 0.0001). However, this deficit becomes significant when one considers the compatibility ratio, whose confidence interval does not include one (CR = 0.6, C.I. = 0.4 - 0.8, P ≤ 0.0001).

4.4 Statistical significance of repeated observations that x = 0

It was observed in 53 of the 78 dose groups that the observed number of cases is zero when the predicted number ranges from about 0.01 to 3 (Table 1). In some of the experiments, the probability of observing at least one cancer is close to one, whereas in others it is very low. Nevertheless, it was troubling not to observe any cancer in 53 dose groups, even though the probability of observing zero in any given group was substantial because the LNTH predicts that about 23 cases (an average of 0.5 case per group) should have been observed in these groups. For a non-statistician, this is akin to observing 53 heads when tossing a coin 53 times.

In dose group (i), there is a probability ($P_{0,i}$) that zero case be observed. Since the outcome in each dose group is independent from that of the others, the probability of observing zero case of cancer in every group is the product of the probabilities ($P_{0,1}.P_{0,2}.....P_{0,53}$) of observing zero case in every one of these 53 dose group. The $P_{0,i}$ values for the 53 dose groups are found in Table 1, and their product is $2.3\ 10^{-43}$. This probability is so close to zero that it is seems improbable that the LNTH should hold under the considered experimental conditions. Research is underway to formalize rigorous statistical analyses of experimental results obtained in various animal species with different radionuclides aiming at different target organs.

5. Conclusions

The incidence of cancer induced by internally deposited alpha emitters was reviewed for a group of 27 animal experiments. Doses of alpha radiation were considered low when they did not shorten the life of the animals, or when no cancer was observed in the exposed animals. The Odds Ratio per unit dose was determined for each dose group, assuming the LNTH holds at all dose levels. The goodness of fit of between the predictions of the LNTH and the experimental results in all the animal experiments may give the impression that the LNTH is a reliable descriptor of the risk of radiogenic cancer under the experimental conditions used by the authors of the studies. However, the observation that the cancer incidence was much lower than predicted in 67 of the 78 dose groups, and was zero in 53 dose groups when more than 22 cancers were predicted by the LNTH is indicative of a need for an in-depth analysis of all the data available on the effects of low doses of radiation. This analysis must not be limited the effects of to high LET radiation.

The analysis of observed and predicted numbers of cancer cases showed that

a) The statistics in any specific dose group or animal experiment were too weak to draw firm conclusions concerning the consistent reality of detrimental effects of low doses of alpha radiation. However, the comparison of pooled observed and predicted cancer incidence data showed that

- In 11 of the 78 dose groups, the observed incidence of cancer in exposed animals was compatible with the LNTH predictions (Table 2). In these eleven groups, the organ doses ranged from 0.02 to 2.08 Gy.

- In the dose group in which the number of cancer cases was smaller than the predicted by the LNTH, the deficit in cancer cases was statistically significant, with $OR_{Obs} \approx 2.4$, compared to $OR_{th} = 5.2$, with some overlap between the OR_{Obs} and OR_{th} confidence intervals (Table 2).

- In the 53 animal experiments in which no cancer cases have been observed when 22.5 were predicted by the LNTH, the incompatibility between observed and predicted numbers of cancer cases was clear (CR = 0.02; C.I. = 0.001 - 0.34; $P < 0.0001$). In these groups of animals, the dose-effect relationship is probably sub-linear and the existence of thresholds cannot be ruled out.

b) The large number of dose groups in which no cancer was observed was subject to a more detailed analysis. In each dose group, there is a well-defined probability that the number of observed cancers be smaller than the number predicted by the LNTH. Since the experiments are independent from each other, the probability of observing zero case when more than zero is predicted is the product of the probabilities of observing zero case in each dose group in which this occurs. The probability of observing zero case in each one of the 53 dose groups, when 22 or 23 were predicted, was $2.3\ 10^{-4}$. Therefore, it seems quasi-certain that there exists doses of internally deposited alpha emitters below which radiogenic cancers are not induced.

This finding is in agreement with the observation of threshold doses in radium dial painters (Thomas 1993), and in Thorotrast patients (Andersson 1992).

c) The indication that the relationship between dose and cancer induction is sub-linear, and that threshold-like doses are likely to exist is not immediately helpful to health physicists or regulators, but it should stimulate the scientific community in its efforts of to determine the real effects of low radiation doses. In any case, it does not seem legitimate to use the LNTH to calculate the hypothetical number of cancers that would be due to a dose increment a fraction of the natural background radiation in a large population.

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Reference	Type of experiment	No. of controls	No. of cancers in controls	Radio-nuclide	Dose (Gy)	No. of exposed animals	Observed no. of cases (x)	Predicted no. of cases (x_{th})	p(x,D)	Goodness of fit R
Sanders 1993	Bone cancer in rats after inhalation of Pu oxide	1052	2	PuO_2	0.06	1389	2	5.68	0.004	1.00
					0.19	343	3	3.20	0.60	
					0.62	145	1	3.80	0.11	
					2.32	58	4	3.40	0.37	
Mays 1987	Bone cancer in dogs after injection of a radionuclide	146	1	Am-241	0.06	14	0	0.32	0.73	0.98
					0.22	14	1	0.91	0.77	
					0.58	13	2	2.08	0.65	
				Ra-228	0.93	12	0	1.19	0.28	
					2.39	12	1	2.92	0.17	
				Ra-226	0.27	10	0	0.20	0.82	1.00
					0.80	25	1	1.15	0.98	
					1.66	23	2	1.96	0.87	
					3.56	14	2	2.45	0.24	
				Pu-239	0.02	20	1	0.43	0.93	0.99
					0.05	38	1	1.66	0.50	
					0.15	23	3	2.70	0.72	
				Th-228	0.13	13	0	0.78	0.45	0.99
					0.39	12	2	2.00	0.68	
					1.13	12	5	5.64	0.99	
White 1994	Bone cancer in dogs after injection of Ra-226	158	4	Ra-226	0.90	46	0	2.92	0.05	0.99
					3.00	38	4	5.83	0.29	

Table 1 . Comparison of observed and predcited numbers of cancer cases in animals after intake of alpha emitting radionuclides. (x = observed number of cases; x_{th} = number of cases predicted by the linear no threshold hypothesis; p(x,D) = probability that x number of cases be observed at dose D).

Reference	Type of experiment	No. of controls	No. of cancers in controls	Radio-nuclide	Dose (Gy)	No. of exposed animals	Observed no. of cases (x)	Predicted no. of cases (x_{th})	p(x,D)	Goodness of fit R
Taylor 1983	Bone cancer in C57Bl/Do black female mice after injection of a radionuclide	87	1	Ra-226	0.38	12	0	0.19	0.83	0.89
					2.32	12	0	0.44	0.63	
					6.40	12	0	0.98	0.36	
				Pu-239	0.06	12	1	0.24	0.79	0.98
					0.47	12	1	0.89	0.78	
					1.23	12	1	2.10	0.30	
				Am-241	1.76	10	1	0.93	0.39	1.00
					5.19	12	3	3.03	0.64	
				Cf-249	0.12	12	0	0.25	0.78	0.90
					0.65	12	1	0.74	0.84	
					1.50	11	1	1.39	0.59	
				Cf-252	0.20	12	0	0.21	0.81	0.92
					1.10	10	0	0.43	0.65	
					3.17	11	0	1.11	0.31	
Taylor 1983	Bone cancer in C57Bl/Do black male mice after injection of a radionuclide	94	0	Ra-226	0.40	12	0	0.04	0.96	1.00
					2.56	12	0	0.28	0.76	
				Pu-239	0.10	12	0	0.05	0.95	0.95
					0.67	11	0	0.32	0.76	
					1.62	12	0	0.84	0.42	
				Am-241	1.70	1	0	0.33	0.72	0.90
					4.57	11	0	0.88	0.40	
				Cf-249	0.11	11	0	0.04	0.97	0.99
					0.64	10	0	0.18	0.84	
					2.08	12	1	0.70	0.85	
				Cf-252	0.20	12	0	0.08	0.92	0.83
					1.27	12	0	0.51	0.59	
					3.43	13	0	1.49	0.21	

Table 1 (cont'd-1). Comparison of observed and predcited numbers of cancer cases in animals after intake of alpha emitting radionuclides. (x = observed number of cases; x_{th} = number of cases predicted by the linear no threshold hypothesis; p(x,D) = probability that x number of cases be observed at dose D).

Reference	Type of experiment	No. of controls	No. of cancers in controls	Radio-nuclide	Dose (Gy)	No. of exposed animals	Observed no. of cases (x)	Predicted no. of cases (x_{th})	p(x,D)	Goodness of fit R
Taylor 1983	Bone cancer in C57Bl/Do albino male mice after injection of a radionuclide	60	0	Ra-226	0.39	10	0	0.01	0.99	1.00
					2.33	15	0	0.05	0.96	
					5.77	18	0	0.16	0.09	
				Pu-239	0.10	13	0	0.06	0.98	0.98
					0.55	16	0	0.11	0.90	
					2.04	12	0	0.30	0.73	
				Am-241	0.09	16	0	0.01	0.99	0.99
					0.58	14	0	0.07	0.93	
					1.63	16	0	0.22	0.80	
				Cf-249	0.14	15	0	0.02	0.98	0.98
					0.59	14	0	0.03	0.97	
					3.07	16	0	0.16	0.85	
					6.19	20	0	0.40	0.67	
				Cf-252	0.24	15	0	0.02	0.98	0.98
					1.35	17	0	0.14	0.87	
					3.52	17	0	0.36	0.70	
Taylor 1983	Bone cancer in C57Bl/Do albino female mice after injection of a radionuclide	58	0	Ra-226	0.37	15	0	0.04	0.96	0.98
					2.31	12	0	0.19	0.83	
					7.43	11	0	0.57	0.57	
				Pu-239	0.08	16	0	0.19	0.83	0.93
					0.43	17	0	1.06	0.33	
					1.32	16	4	3.08	0.82	
				Am-241	0.09	16	0	0.08	0.92	0.93
					0.52	16	0	0.47	0.62	
					1.68	14	0	1.32	0.25	
				Cf-249	0.11	17	0	0.07	0.94	0.99
					0.79	16	0	0.44	0.64	
				Cf-252	0.20	15	0	0.09	0.92	0.98
					1.21	14	0	0.48	0.61	
					3.42	15	0	1.46	0.82	

Table 1 (cont'd-2) . Comparison of observed and predcited numbers of cancer cases in animals after intake of alpha emitting radionuclides. (x = observed number of cases; x_{th} = number of cases predicted by the linear no threshold hypothesis; p(x,D) = probability that x number of cases be observed at dose D).

Comparison of observed vs predicted number of cancers cases	No. of dose groups	Exposed or controls	No. of animals	No. of cancers		OR_{Obs} (Observed vs controls)	OR_{th} (Predicted vs observed)	CR (Compatibilty ratio - Predicted vs observed)	Compatible with LNTH?
				Observed	Predicted				
$x >= x_{th}$	11	Exposed	166	18	14.6	12.6 (3.0 - 54.0) p<0.0001	11.5 (2.6-51) p<0.0001	1.2 (0.6 - 2.5) p=0.7)	yes not significant
		Controls	233	2	2				
$x < x_{th}$	67	Exposed	2887	33	70.8	2.4 (1.1 - 5.1 p=0.035)	5.2 (2.5 - 11.0 p<0.0001)	0.4 (0.24 - 0.55 p<0.0001)	no, but C.I. for Or_{th} and OR_{Obs} overlap
		Controls	1655	8	8				
x=0	53	Exposed	730	0	22.5	0.06 (0.003 - 1.1 p=0.008)	3.2 (1.3 - 8.0 p=0.008)	0.02 (0.001 - 0.34 p<0.0001)	no
		Controls	603	6	6				
All	78	Exposed	3041	49	83.4	3.3 (1.6 - 7.0 p=0.001)	5.8 (2.8 - 12.0 p<0.0001)	0.06 (0.04 - 0.8 p=0.004)	no
		Controls	1655	8	8				

Table 2 . Comparison Between Observed and Predicted Numbers of Cancer Cases in Animals at Low Doses of Alpha Radiation.

$x => x_{th}$: the observed number of cancers in exposed animals is equal or larger than the number predicted by th

$x > x_{th}$: the observed number of cancers in exposed animals is smaller than the number predicted by the LNTH

x=0 : no cancer observed in the exposed animals

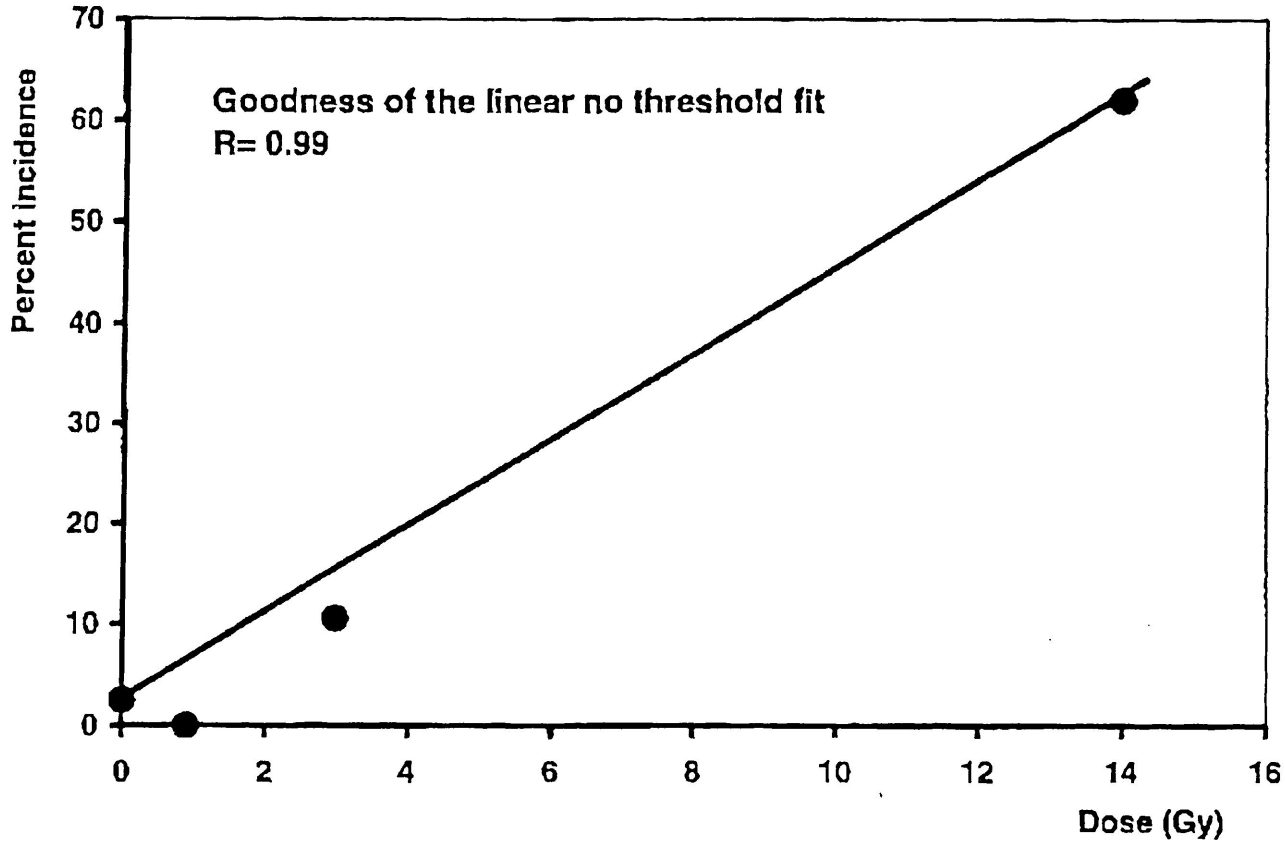

Figure 1 . Percent Cancer Incidence in Dogs After Injection of Ra-226 (White 1994)