

Consistency of The Mortality of Chronically-irradiated Beagles with the Linear No-Threshold Model

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Abstract

This note explores whether the lowest dose-rate mortality data from the beagle tissue archive might be consistent with the Linear No-Threshold (LNT) Model and might give evidence in favour of that model. I suggest that the answer may be 'yes'; further statistical analysis will be required to establish how strongly the data favour LNT over alternative non-linear models.

1 The mortality data

A paper by Fliedner et al. (2012) presents interesting data adapted from Fritz (2002) showing the mortality curves of dogs after whole-body chronic gamma-irradiation at various dose-rates. These curves have been obtained from the beagle tissue archive¹, which preserves the results of experiments in which hundreds of dogs were chronically exposed to gamma radiation for their entire lives Carnes and Fritz (1993). The dose-rates to the whole body were 3 mGy/day, 7.5 mGy/day, 18.8 mGy/day, 37.5 mGy/day, 75 mGy/day and 127.5 mGy/day, 262.5 mGy/day, 375 mGy/day and 640 mGy/day. A control group received no gamma radiation.

In the high dose-rate groups (540 mGy/day, 375 mGy/day and 262.5 mGy/day), all observed deaths were caused by hemopoietic failure. In the middle dose-rate groups (127.5 mGy/day, 75 mGy/day and 37.5 mGy/day), deaths are caused by hemopoietic insufficiency with septicemia and aplasia or myeloproliferative disorders and fatal tumours. At dose rates below

¹http://janus.northwestern.edu/dog_tissues/

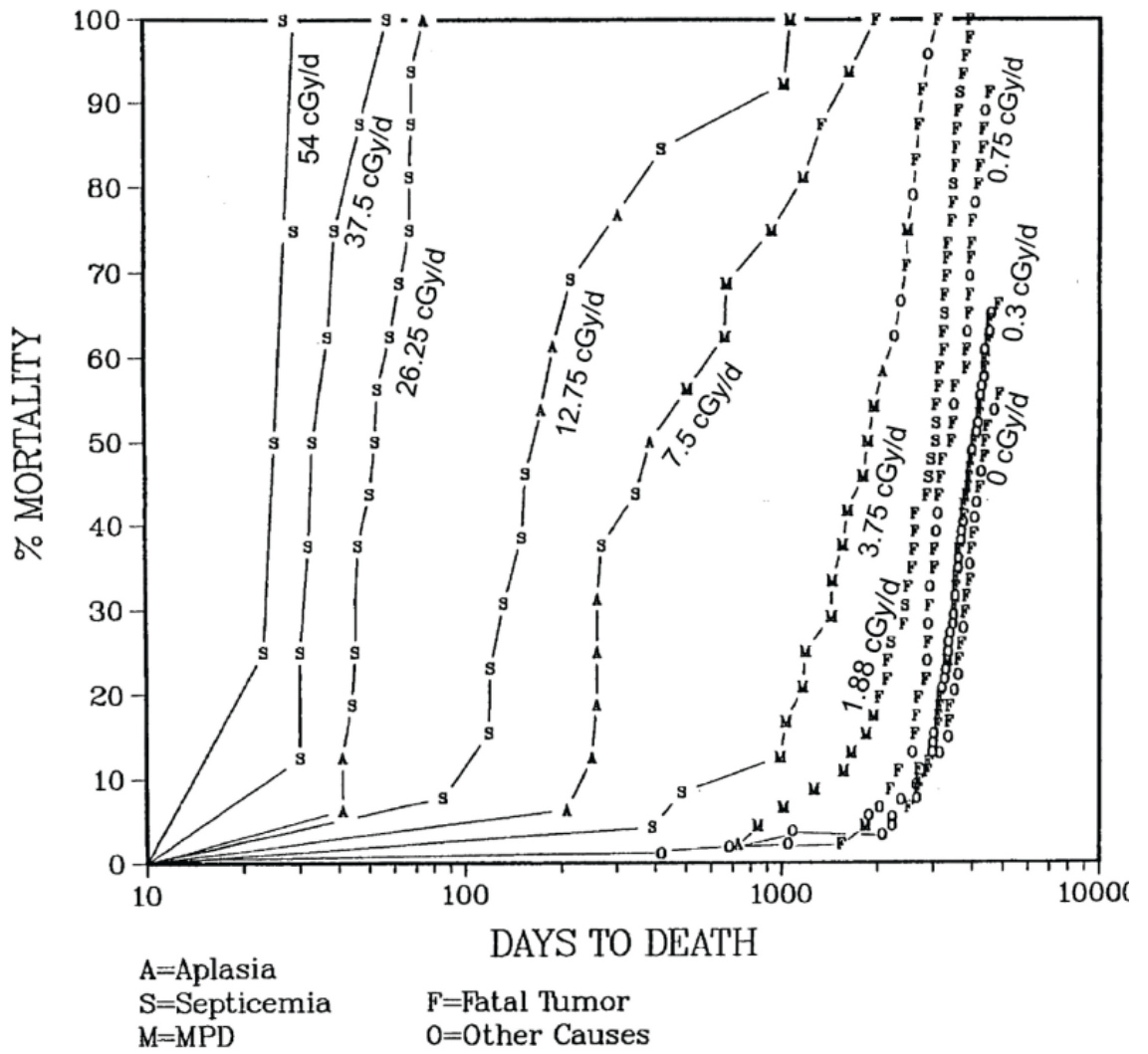


Figure 1: Mortality curves of dogs after whole-body chronic gamma-irradiation at various dose-rates in cGy/day, adapted from (Fritz 2002). (FIGURE 3 from Flidner et al. (2012).)

18.8 mGy/day, and in the control group, a large fraction of the deaths are from fatal tumours.

The lowest dose rate in the experiment, 3 mGy/day (equivalently 90 mGy/month, or 1100 mGy/year), is not a “low dose rate” by current health protection standards (which limit the annual dose of industry workers in the USA and the UK to 50 mSv/year and 20 mSv/year respectively), but it *is* lower than the 100 mSv/month dose rate that has been identified by some critics of those health protection standards (eg Allison (2009)) as a rough threshold below which radiation might be deemed to have negligible harm to most humans. Wade Allison also criticises the use of the ‘Linear No Threshold’ (LNT) model of radiation-harm in policy making, and suggests that there *is* a threshold, somewhere near a dose rate of 100 mSv/month, below which the harm from radiation is significantly less than the Linear No Threshold hypothesis would predict (Allison, 2009).

It is therefore interesting to study the beagle data at the lowest dose rates of 3 mGy/day, 7.5 mGy/day, and 18.8 mGy/day, and the control group, to see whether these data seem compatible with the Linear No Threshold hypothesis, and whether they favour LNT over other models.

I intend to conduct a proper statistical investigation of this question in due course. This technical note describes preliminary manual model-fitting to see whether the effects that seem to be present in the data are roughly consistent with a simple version of the Linear No Threshold model.

Of course, humans are not beagles, and it is not clear how advocates of the pro-LNT and anti-LNT hypotheses would predict that these hypotheses should be transformed between species with different body masses and different metabolic rates.

2 The model

I simulated a simple model in which the death of a dog is caused either “by natural causes” *or* by a radiation-induced cancer. (This model is not intended to capture the higher-dose-rate causes of death; it is just a model for low dose-rates.)

The model \mathcal{H}_{LNT} treats the two causes of death independently as follows.

The probability that a dog is still surviving at age t , in a radiation field of intensity r is:

$$P_{\text{Alive}}(t | r, p, q, \mathcal{H}_{\text{LNT}}) = S_{\text{Natural}}(t) \times S_{\text{RadiationInducedCancerDeath}}(t) \quad (1)$$

where $S_{\text{Natural}}(t)$ is the probability, in the absence of the radiation, that a dog would survive at least to time t , and $S_{\text{RadiationInducedCancerDeath}}(t)$ is the probability, in the absence of natural death, that a dog would not have died from a radiation-induced cancer by time t .

The natural-death survival function is, as a first stab, a Gompertz–Makeham function

$$S_{\text{Natural}}(t | a, b, c) = \exp\left(-at - \frac{b}{c}(e^{ct} - 1)\right); \quad (2)$$

the parameters found to best fit the control-group data were $a=0/\text{year}$, $b=0.0041/\text{year}$, and $c=0.32/\text{year}$.

The radiation survival function $S_{\text{RadiationInducedCancerDeath}}(t)$ was defined with a two-parameter model. The body is modelled as the union of a large number N of compartments, each of which has three states: healthy (1), pre-cancerous (2), and dead (3). Initially all compartments are healthy. At every time-step each healthy compartment has a probability of turning pre-cancerous $p_{1 \rightarrow 2}$ that depends on the radiation dose $D \delta t$ in that timestep:

$$p_{1 \rightarrow 2} = \lambda \times D \delta t \times \frac{m}{N}, \quad (3)$$

where λ is the dose-sensitivity (essentially the ‘linear’ parameter of LNT), D is the dose rate in Sv per unit time, m is the mass of the animal, and thus m/N is the mass of one compartment. Pre-cancerous compartments turn dead with probability

$$p_{2 \rightarrow 3} = q \delta t. \quad (4)$$

The two parameters of this model are the dose-sensitivity λ and the fatal-cancer-completion rate q , which is inversely related to the typical latency between a single radiation-induced mutation and the subsequent death from cancer. (The probability that a pre-cancerous compartment reverts to the healthy state was assumed to be zero.)

Given these two parameters, the probability $\mathbf{p}(t) = (p_1(t), p_2(t), p_3(t))$ that a particular compartment is in state (1,2,3) can be computed, and the probability that the animal has *no* fatal radiation-induced cancers is

$$S_{\text{RadiationInducedCancerDeath}}(t) = (1 - p_3(t))^N, \quad (5)$$

where N is the number of compartments. To be clear, the assumption is that if any compartment is dead, the animal is dead.

2.1 Analytic solution for the radiation survival function

(This subsection can be skipped.)

The three-compartment model can be solved, yielding

$$1 - p_3(t) = \frac{\frac{\lambda Dm}{N}}{\frac{\lambda Dm}{N} - q} e^{-qt} - \frac{q}{\frac{\lambda Dm}{N} - q} e^{-\frac{\lambda Dm}{N}t} \quad (6)$$

and thus in the limit of large N we can obtain

$$S_{\text{RadiationInducedCancerDeath}}(t) = \lim_{N \rightarrow \infty} (1 - p_3(t))^N \quad (7)$$

$$= \exp\left(-\lambda Dm \left[t - \frac{1}{q} (1 - e^{-qt})\right]\right) \quad (8)$$

$$= \exp\left(-\lambda Dmt + \frac{\lambda Dm}{q} (1 - e^{-qt})\right) \quad (9)$$

$$= \exp\left(-\lambda Dmt - \frac{\lambda Dm}{q} (e^{-qt} - 1)\right), \quad (10)$$

which looks like a Gompertz–Makeham function (2), except that the sign in the final exponent e^{-qt} here is negative rather than positive.

(End of skippable subsection.)

2.2 Method – part 1

I manually adjusted the parameters λ and q to see if the qualitative features of the raw data could be reproduced – in particular I was interested in the small gap that the data seem to show between the control group’s mortality curve and that of the 3-mSv/d group. The gap between the medians of the curves corresponds to a loss of life of roughly 5% of the median beagle-lifespan. (I will assess in part 2 the statistical significance of this gap.)

Roughly what gap would the LNT hypothesis predict?

To answer this question, we need the parameter λ . In average adult humans, the standard LNT coefficient appears to be 0.05 per whole-body-Sievert. (For example, LNT asserts that an extra dose of 20 mSv to the whole body gives an extra 0.1% chance of fatal cancer.) This implies that for humans my model’s parameter λ should be set to roughly $0.05/\text{Sv}/(80 \text{ kg}) = 0.000625/\text{Sv}/\text{kg}$, assuming a typical human weight of 80 kg. There may be a factor of 2 or so of slop in this coefficient, since the LNT hypothesis is often accompanied by a “dose and dose-rate effectiveness factor”

(DDREF) which scales down the coefficient at low dose-rates. (For simplicity, I am assuming here that the fatal-cancer-completion rate q in my model is big enough that an induced cancer has a good chance of turning into a fatal cancer within the human's lifetime. If q is too small for this assumption to be true then the statements above about the value of λ need to be reworked; for "small" q , the probability of conversion within a period T such as the remaining period of life is roughly qT , so for "small" q it is λqT that is roughly equal to $0.000625/\text{Sv}/\text{kg}$. Here, q is "small" if $qT \ll 1$.)

Of course, as I said before, humans are not beagles. If $\lambda = 0.000625/\text{Sv}/\text{kg}$ for a human, what should λ be for a beagle, whose body mass (10 kg) is 8 times smaller than a human's and whose lifespan (12 years) is about 6 times smaller?

I don't know the LNT community's answer to this inter-species-translation question, but I imagine that it must lie between the following two hypotheses:

1. All mammals are made of similar tissue, and have similar λ ; thus LNT says $\lambda_{\text{beagle}} \simeq 0.000625/\text{Sv}/\text{kg}$. Note that under this version of the hypothesis, the probability that a beagle will get fatal cancer from a particular dose (measured in Sv) is roughly 8 times *smaller* than the probability for a human, because a human is essentially made up of 8 beagles' worth of tissue, and every beagle-sized chunk has the *same* chance of contracting a fatal cancer.
2. All mammals are similar, in the sense that they have the same chance of contracting fatal cancers when subjected to a particular dose in Sv. This version of the hypothesis asserts that λ_{beagle} is roughly 8 times λ_{human} , ie, $\lambda_{\text{beagle}} \simeq 0.0050/\text{Sv}/\text{kg}$. For this hypothesis to make sense, one could imagine that the relevant target in the body is DNA in cell nuclei; if the number of *cells* is roughly the same in beagles and humans (see Savage et al. (2007) for the truth, which is tissue-dependent), and if the amount of vulnerable DNA per cell is also roughly the same, then the chance of a hit on the target is the same in both species, even though the beagle is smaller.

To summarise, it seems to me that the translation of the LNT hypothesis from humans to beagles would imply λ_{beagle} between $0.000625/\text{Sv}/\text{kg}$ and $0.0050/\text{Sv}/\text{kg}$, assuming q is not 'small'.

If the fatal-cancer-completion rate parameter q is material, we could similarly discuss how it might translate between species. I have the im-

pression that in humans q is believed to be (1/(a few years or possibly decades)). As above, I could imagine that q might be similar for all mammals (if conversion to a fatal cancer depends on biochemical processes that are similar in all mammals); or q might be greater in species with higher metabolic rates and shorter lifespans (if conversion is associated with metabolic processes that run faster in those species). (Mass-specific metabolic rate scales approximately as $m^{-1/4}$; the scaling of cell turn-over rate with body mass appears to depend on the cell type, with some turn-over rates scaling as $m^{-1/4}$ and some scaling as m^0 (Savage et al., 2007); the former scaling law would predict a turn-over rate for beagles 1.68 faster than humans.)

Results – part 1

Figure 2 shows the resulting theoretical curves, alongside an approximate transcription of the original data, when the parameters are set to $q = 1/10.0/\text{year}$ and $\lambda = 0.003125/\text{Sv}/\text{kg}$.

The shapes of the mortality curves are not perfectly matched by the theoretical curves, but the gap between the control group and the 3-mSv/day group (at 50% mortality) is of the same size as the apparent gap in the data.

This indicates that the beagle results are not grossly at variance with the LNT hypothesis and indeed might support it. There is a version of the LNT hypothesis, consistent with the dose-sensitivity for humans, that predicted a measurable effect at 3 mSv/day, of a size similar to the apparent effect size in the data.

2.3 Method – part 2 – how significant is the apparent gap?

Roughly how much statistical uncertainty is there in these mortality curves, given the finite sample size? Let's focus on the identification of the median lifetime of a population from a finite sample of size K . The probability density of the rank of the *true* population-median among K sorted individuals drawn from a population is bell-shaped with a standard deviation of roughly $\frac{1}{2}\sqrt{K}$, so the vertical error bars on the median point of a mortality curve (such as in figure 1) are $\frac{1}{2}\frac{1}{\sqrt{K}}$. The 3-mSv/day group had size $K = 92$ and the control group had $K = 57$. The vertical error bars are thus $\frac{1}{2}\frac{1}{\sqrt{K}} = 0.052$ and 0.066 respectively. These standard deviations can be translated into a standard deviation on the gap between the two curves using the rough slope of the mortality curves at the median, which is about 0.11/year; whatever the true gap is between the true

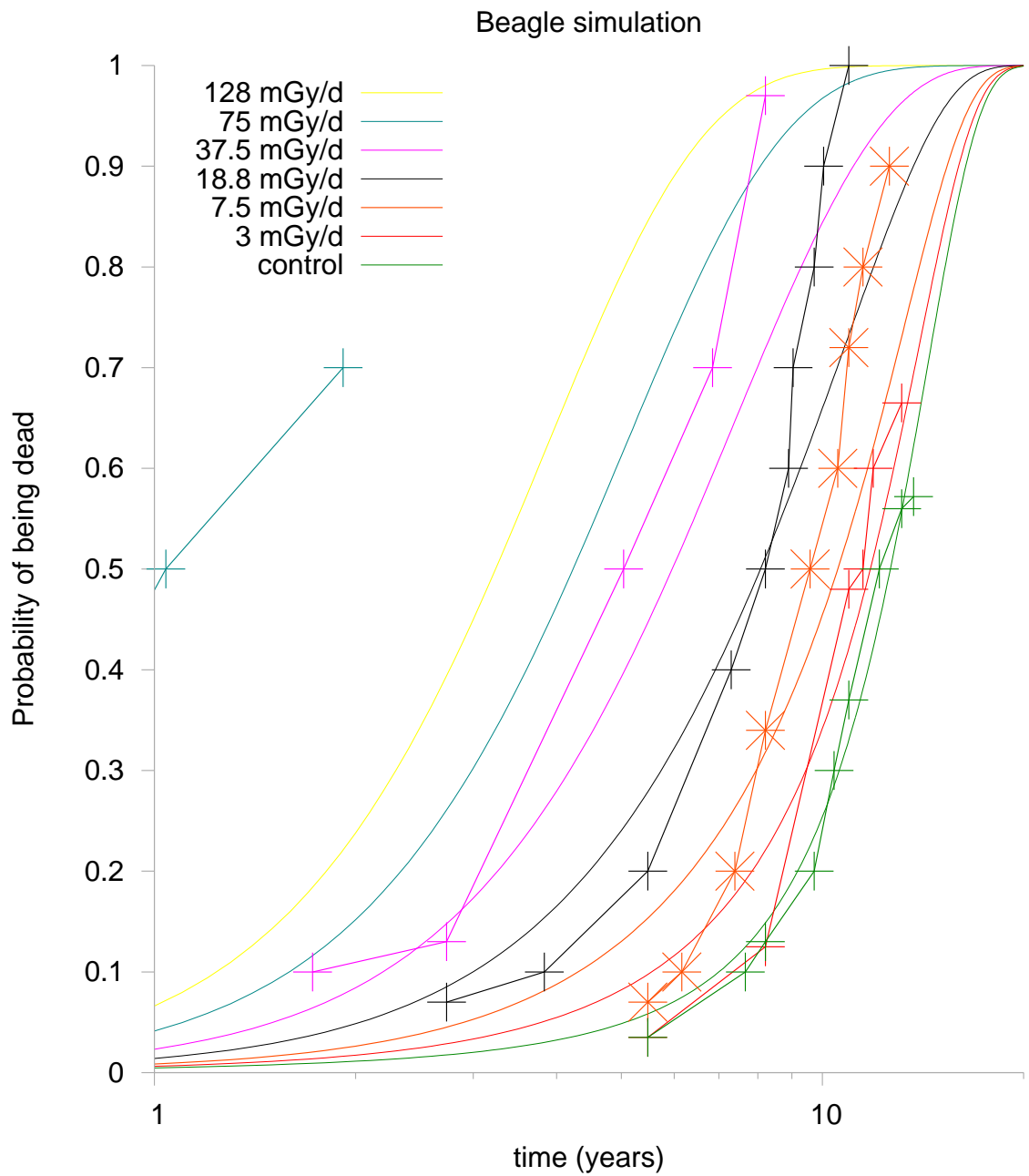


Figure 2: The curved lines show a simple theoretical model of dog mortality with parameters $q = 1/10.0$ and $\lambda = 0.003125/\text{Sv}/\text{kg}$ [computed using $N = 1000$ compartments]; the data points have been transcribed roughly from the original data shown in Figure 1. (Best viewed in colour.)

population medians, an experiment using cohorts of sizes 57 and 92 will give an empirical gap whose standard deviation around the true value is roughly $\sqrt{0.052^2 + 0.066^2}/(0.11/\text{year}) \simeq 0.76$ years (or 277 days). The observed gap between the two cohorts' medians is about 240-300 days (based on eyeballing figure 1). (I will get the original data in due course.) So the observed gap is similar in size to the standard deviation.

In conclusion, the weight of evidence for LNT provided by the observed gap between the two medians (for 3 mSv/day and 0 mSv/day) is weak, not strong.

However, the full data-set includes much more information than the medians, and it is possible that a full statistical model, modelling the known cause of death of every animal, might give weightier results.

What about 7.5 mSv/day?

Applying the same analysis to the comparison of medians of the control group and the 7.5 mSv-day group (of size $K = 46$), the standard deviation of the gap about its true value is roughly $\sqrt{0.074^2 + 0.066^2}/(0.11/\text{year}) \simeq 0.9$ years (or 326 days), and the observed gap is about 940 days. This observed gap between the 7.5 mSv/day group and the control group thus seems highly significant.

3 Acknowledgements

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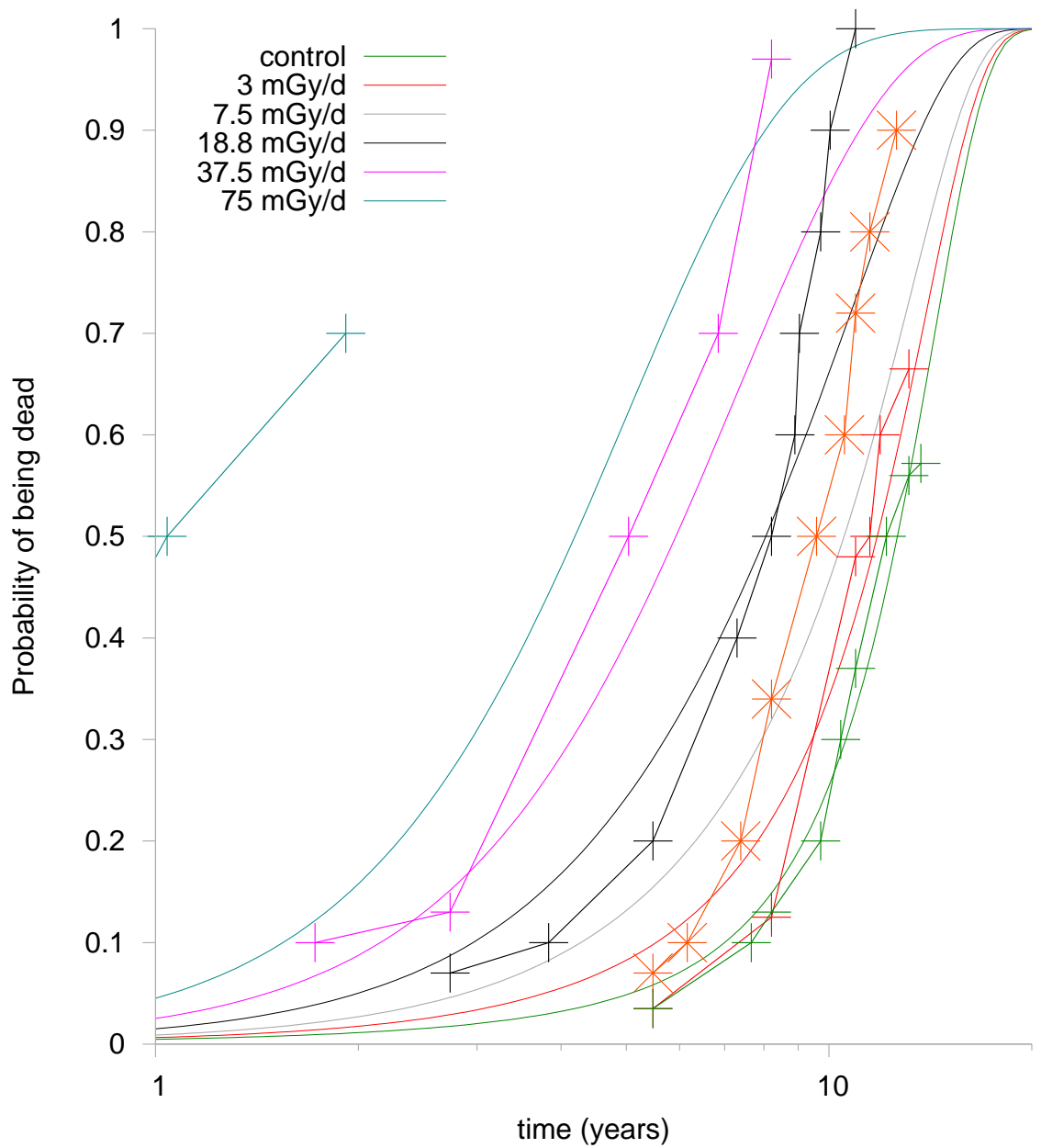


Figure 3: (Replotted using analytic solution.) The curved lines show a simple theoretical model of dog mortality with parameters $q = 1/10.0$ and $\lambda = 0.003125/\text{Sv}/\text{kg}$; the data points have been transcribed roughly from the original data shown in Figure 1. (Best viewed in colour.) (Whereas Figure 2 showed results computed for $N = 1000$ compartments, these curves use the analytic solution for $N \rightarrow \infty$ (equation 9).