

Comparison of 5 Stopping Rules and 2 LD50 Estimators Using Monte Carlo Simulation

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Attached are graphs presented at an ICCVAM meeting in January 2000.

Note the following:

1. For these graphs, the maximum number that could be tested was set at 25. Currently we propose to set the maximum at 15.
2. The test doses were not constrained to a range such as 1 to 5000 units, as in later simulations and as in our current guideline proposal.
3. The graphs include consideration of 2 stopping rules that were subsequently abandoned. The number of stopping rules has been retained, so that Rules number 1, 2, and 5 in later work correspond to the procedures here with the same numbers.
4. While here we do illustrate the use of an LR stopping rule, it is not precisely the rule proposed in the current guideline. The procedure in the current guideline is more simple, uses fewer animals, and results in better precision.

LD50 Estimators Evaluated:

- Maximum likelihood estimator, slope = 2
-
- Geometric average dose (animals at/following reversal).

Stopping Rules Evaluated:

1. Fixed nominal sample size of 6
 2. Stop after 5 reversals.
 - 3a. Convergence of estimators:
 $0.5 < [\text{estimate 1}] / [\text{estimate 2}] < 2$

estimate 1 = geometric average dose;
estimate 2 = MLE with slope=0.5
 - 3b. Like 3a but "factor" of #5 instead of #2.
 4. For H:LD50=GM versus H:LD50=GM/2 (or H:LD50=GM*2),

profile likelihood ratio = 2
- Nominal sample size = 6; Number tested capped at 15 or 25

Performance Measurement based on Monte Carlo

- Bias index
median estimate / true value
?Acceptable . 0.8 - 1.2 X (or .20% bias)
- Spread Index
Ratio of high and low percentiles P95 / P5

?Acceptable . 3-4 X
- Numbers tested (mean, 95th percentile)

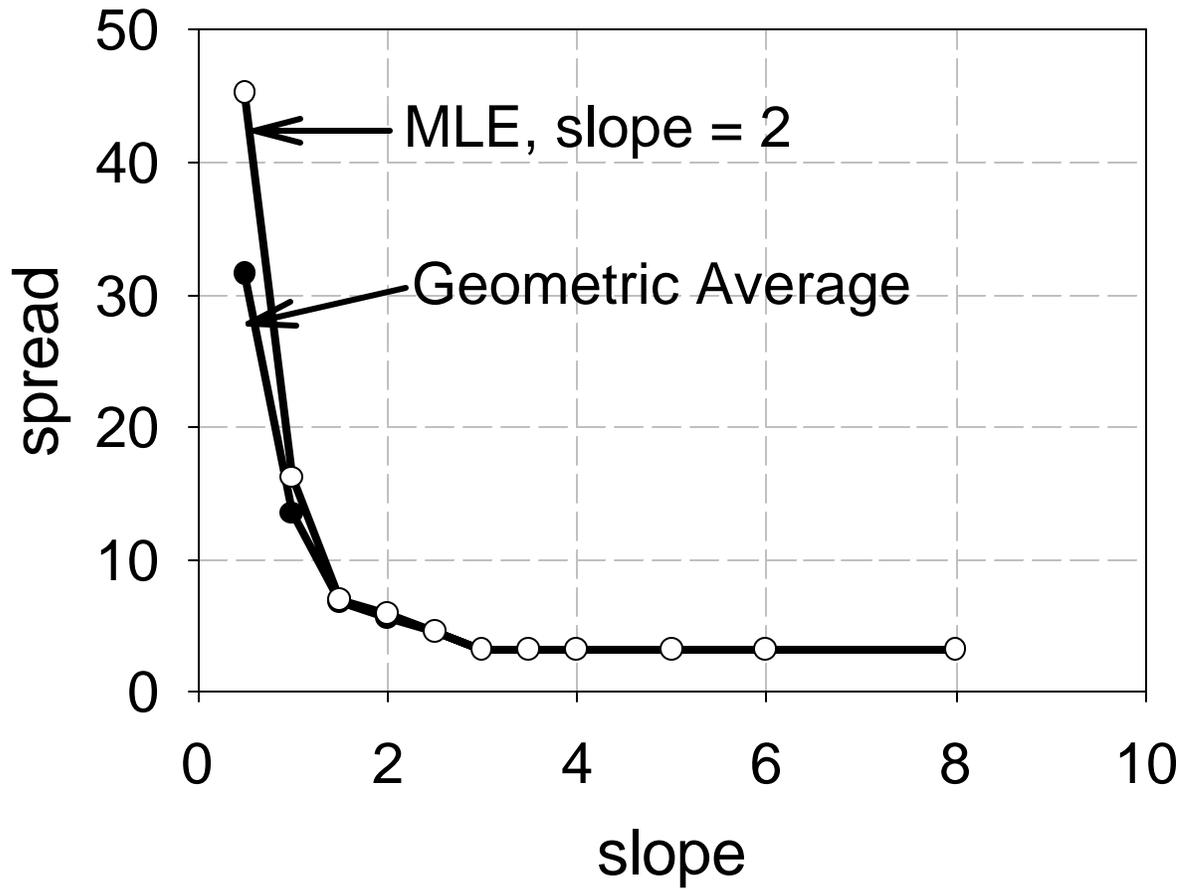
Design of Monte Carlo Study

- True LD50 = 1500 units
- Initial dose 15, 100, 150, 1000, 1500
- Probit slope 0.5 - 8
- Max. number tested 15, 25

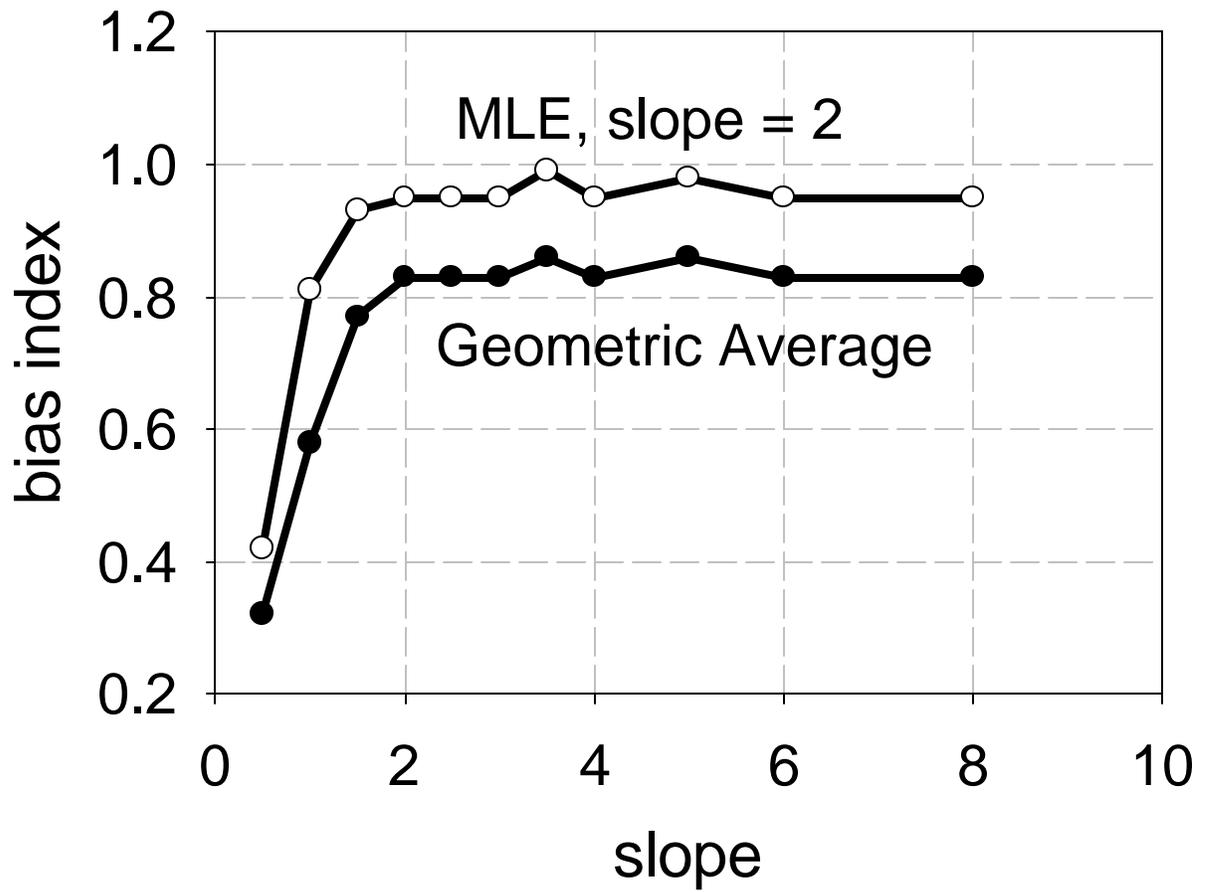
Graph Sets

- Comparison of 2 estimators based on stopping criterion 4 with max tested = 25
- Comparison of stopping criteria 1 and 4 based on geometric mean, max tested = 25
- Comparison of max. tested 15 versus 25 based on stopping criterion 4 and geometric mean.

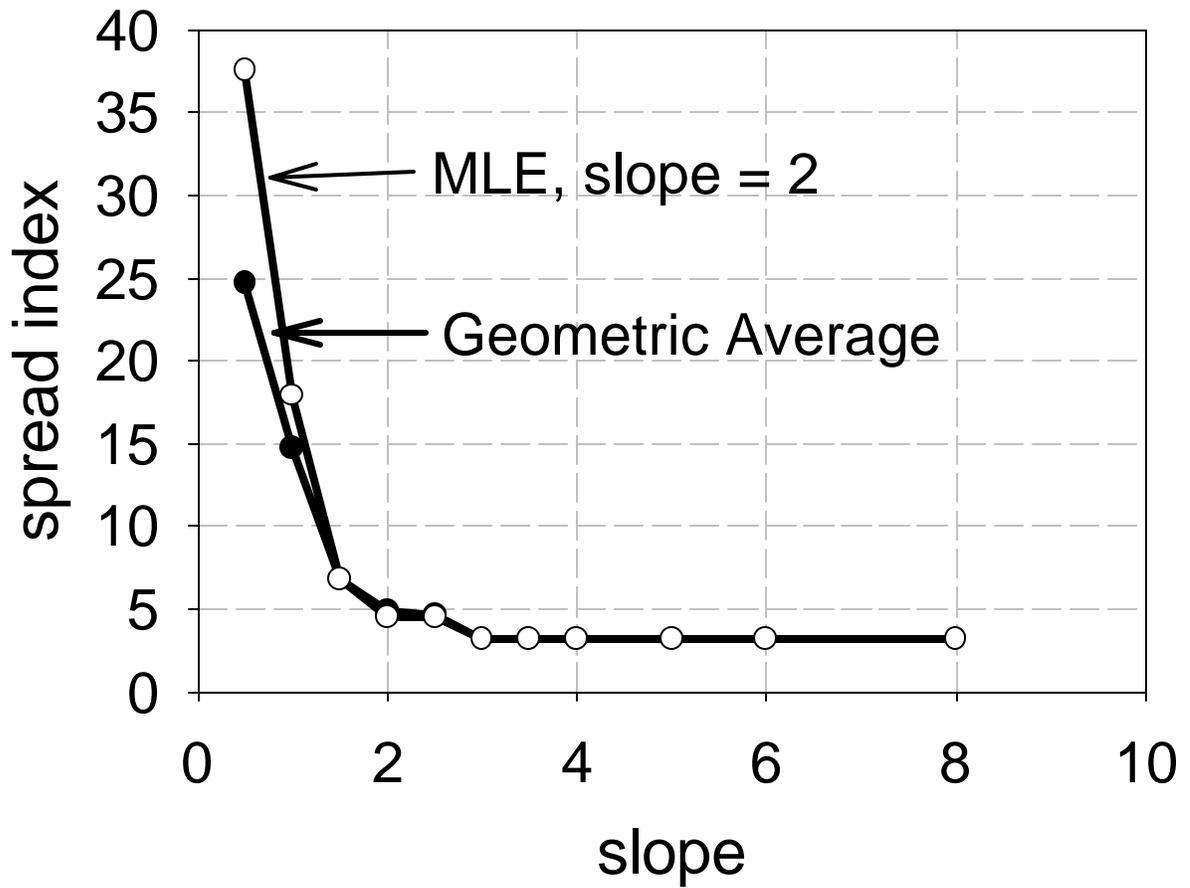
Initial Dose = LD50 / 100



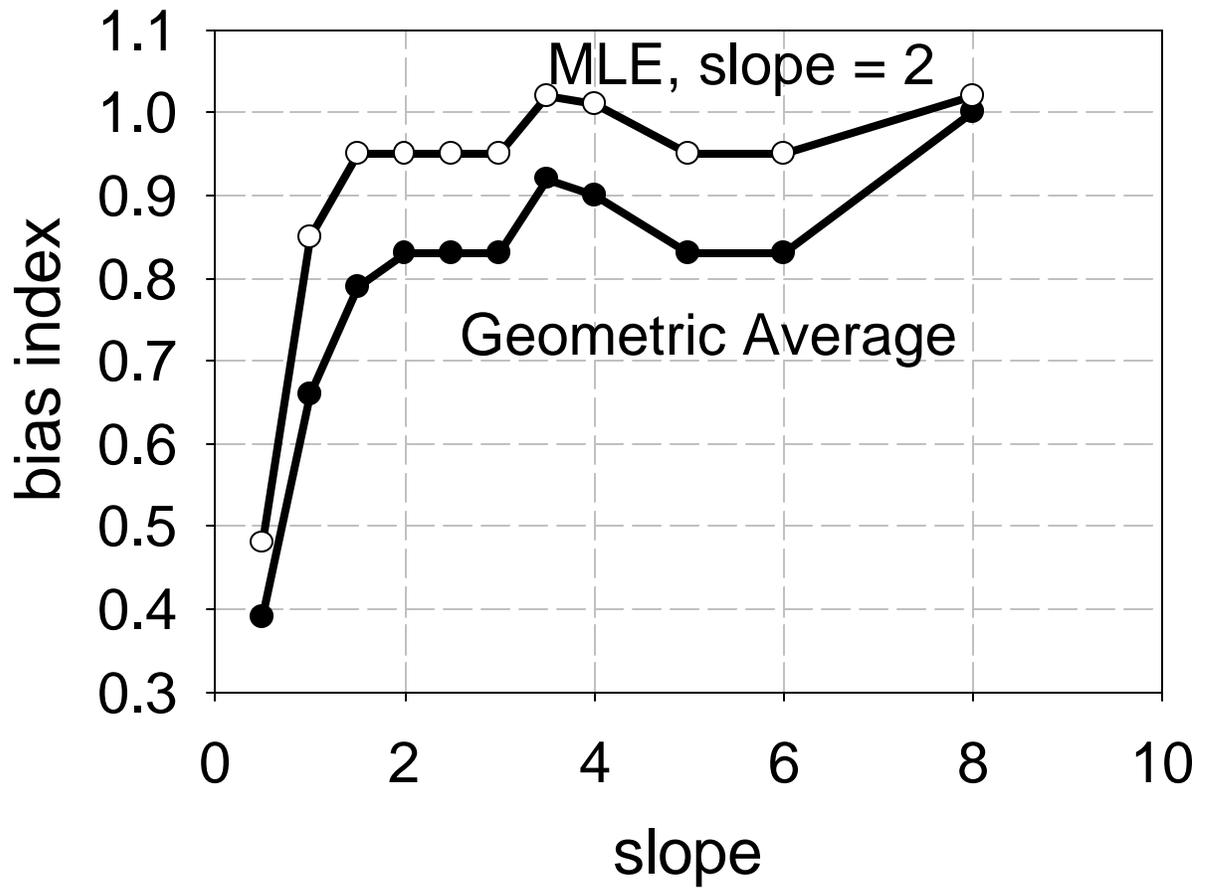
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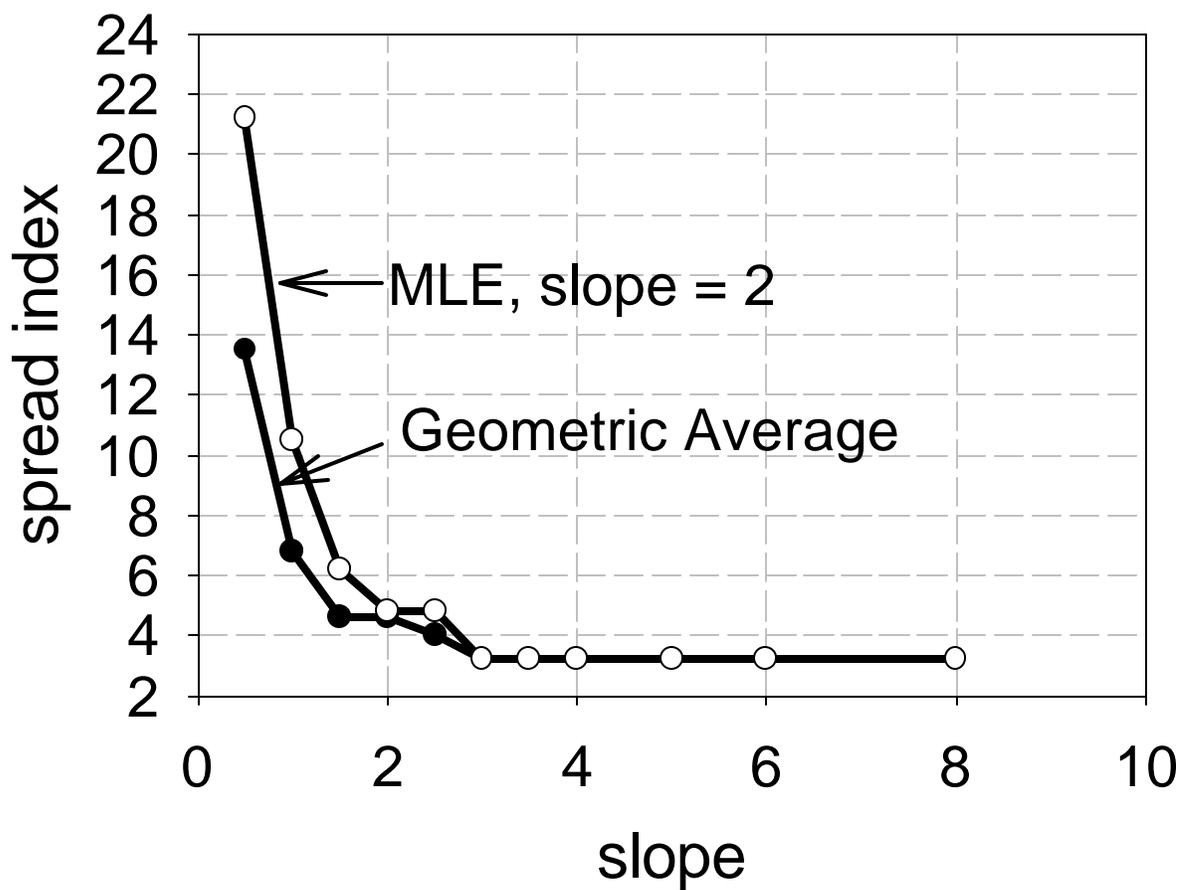
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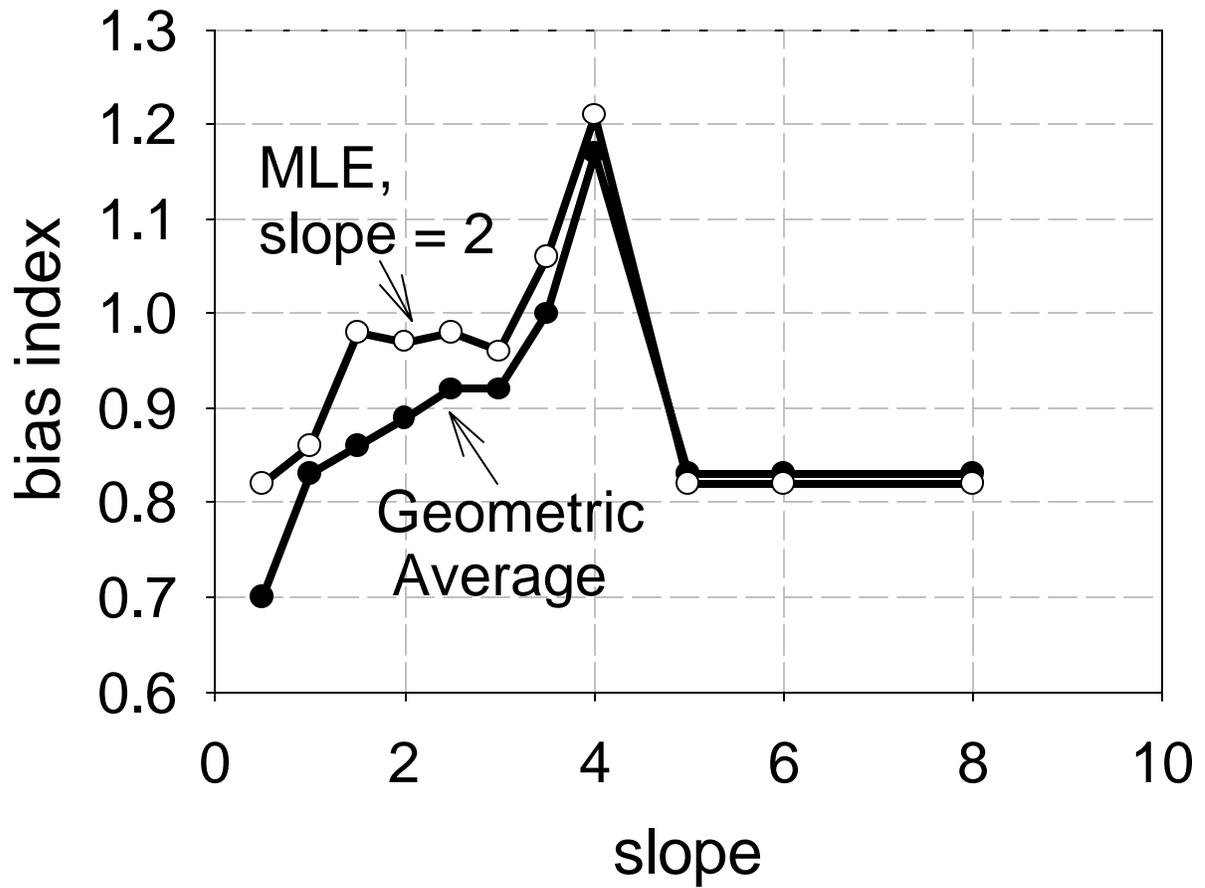
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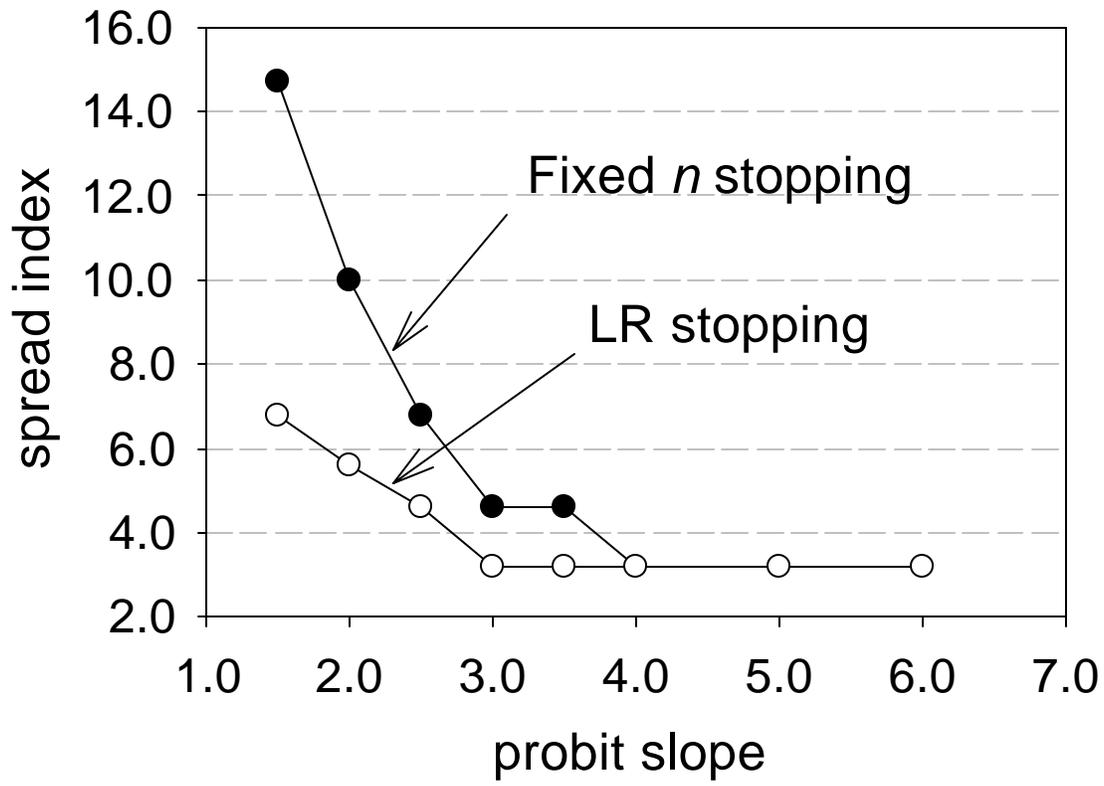
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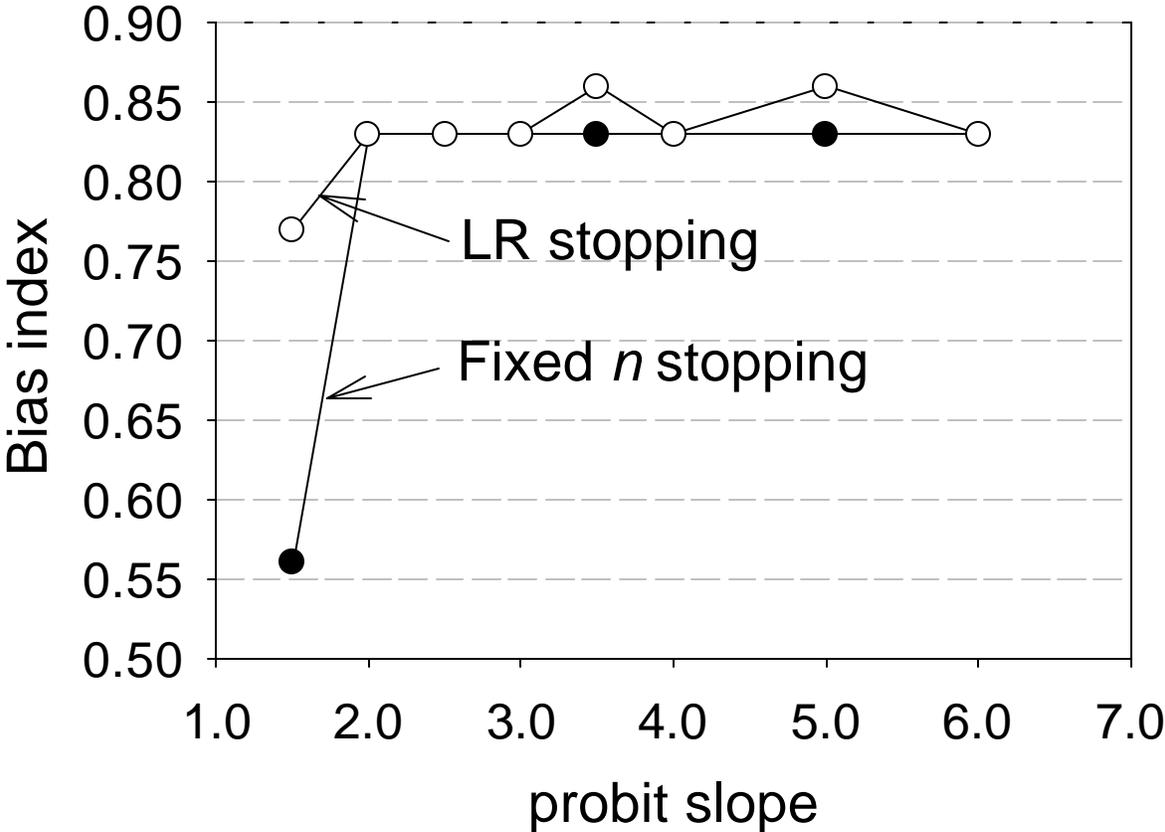
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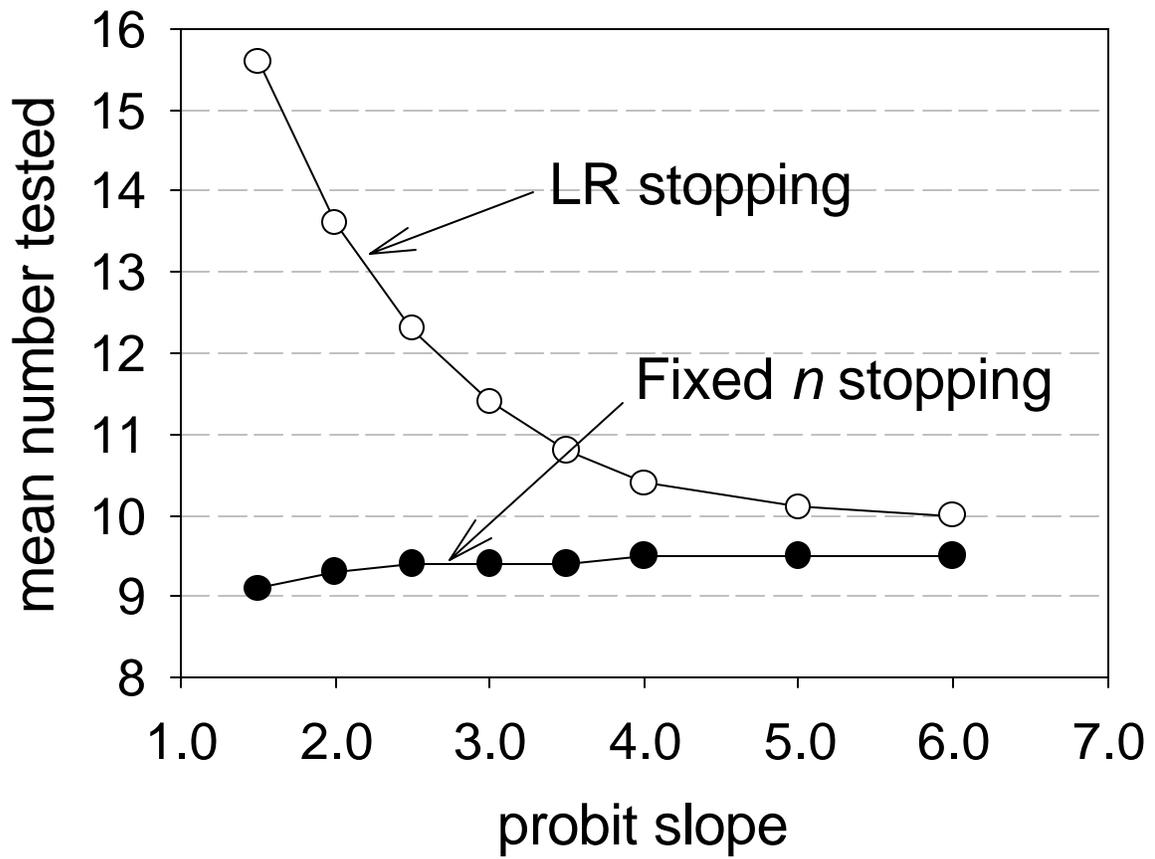
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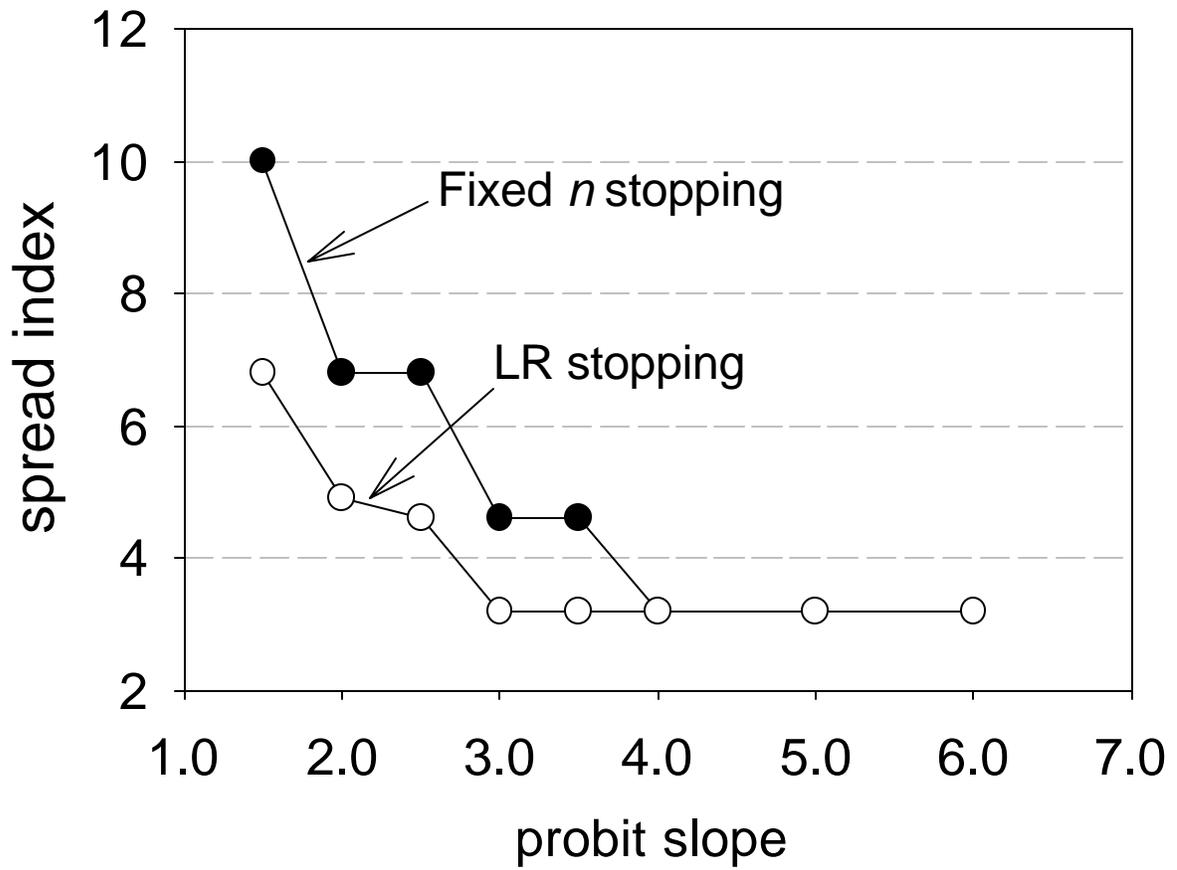
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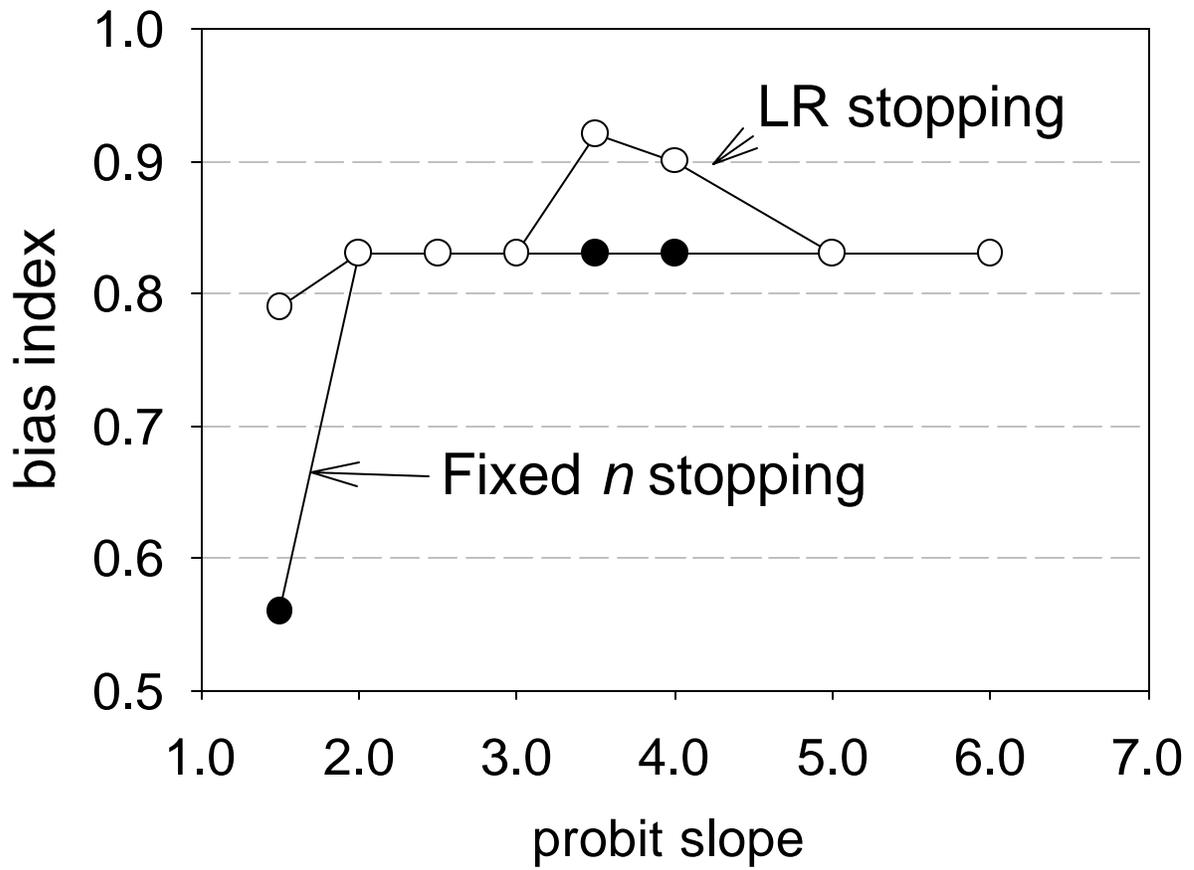
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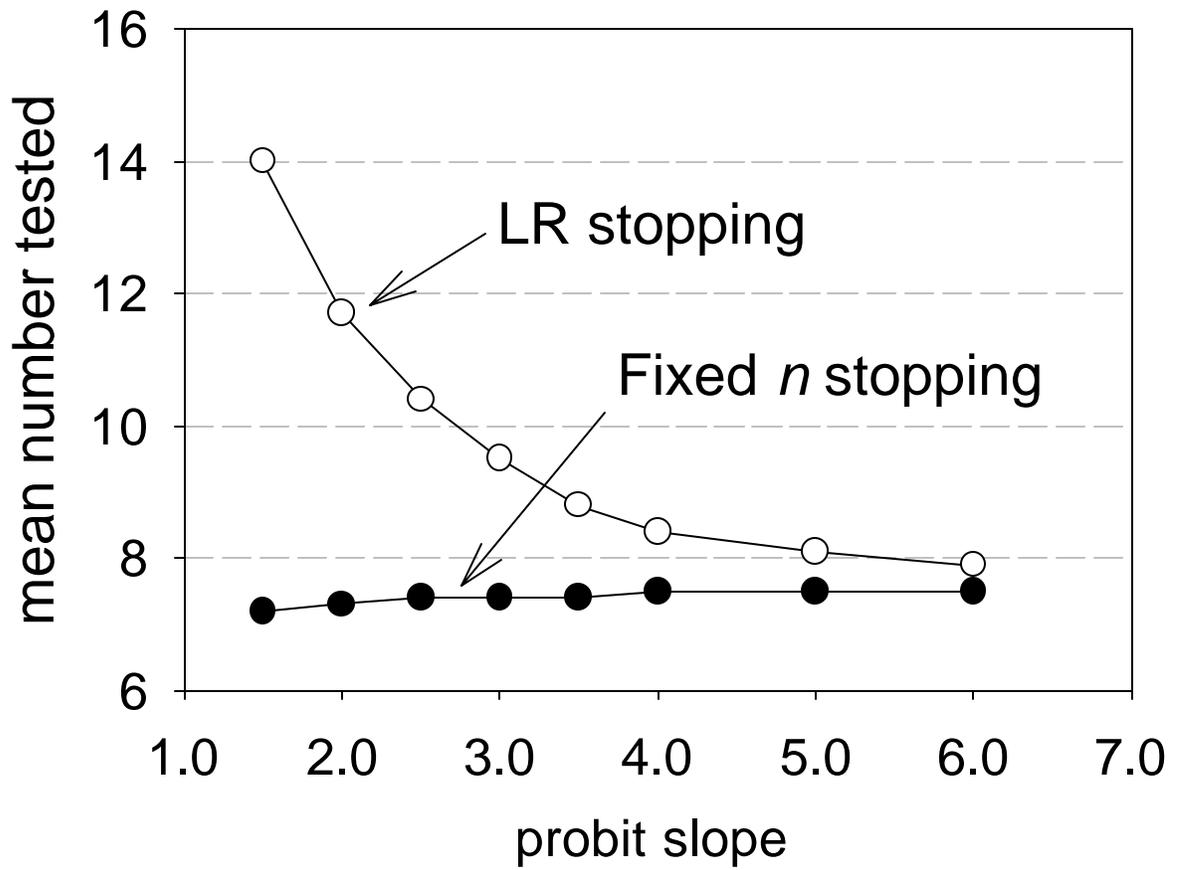
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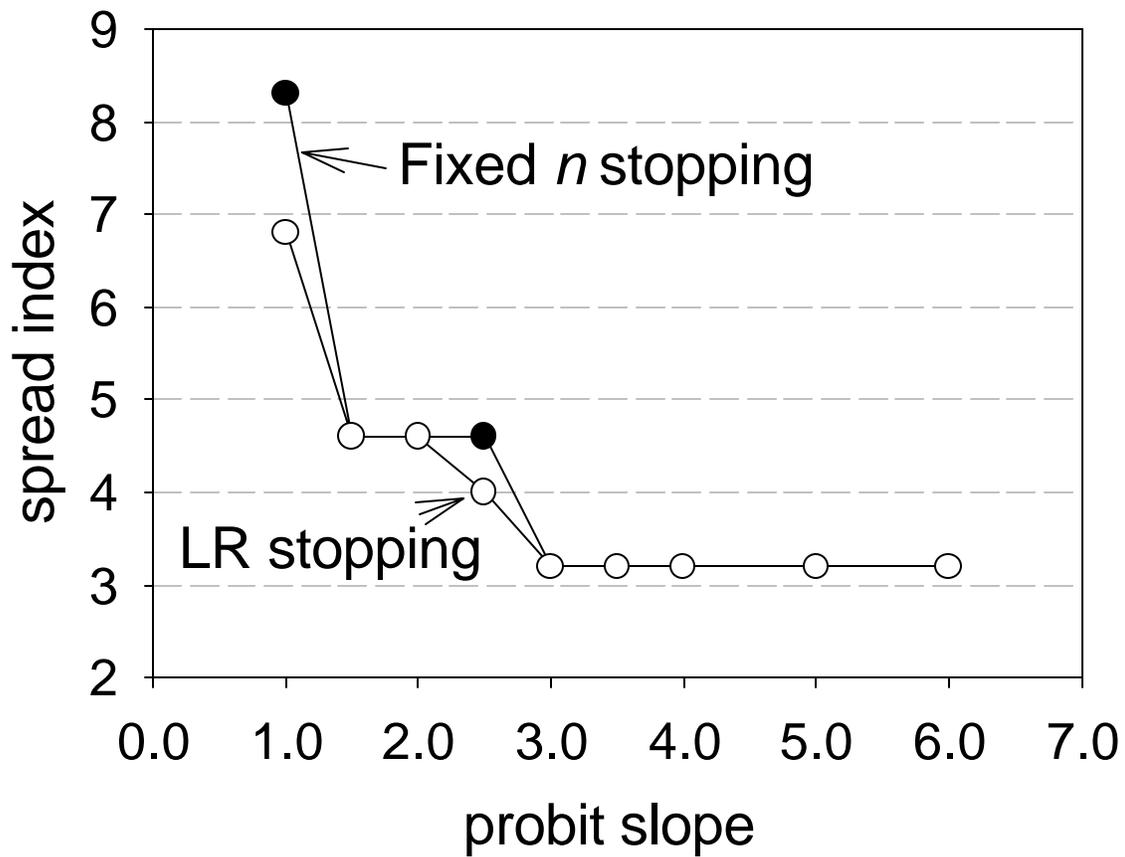
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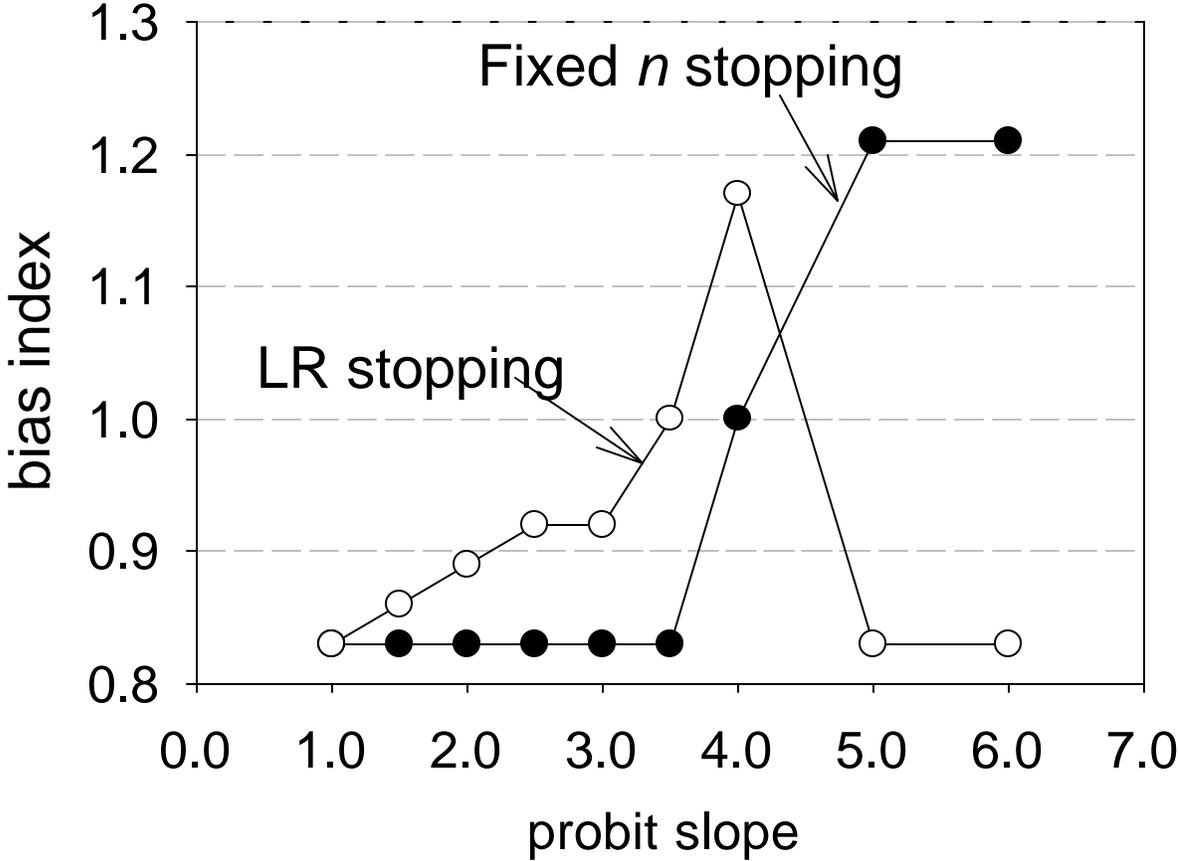
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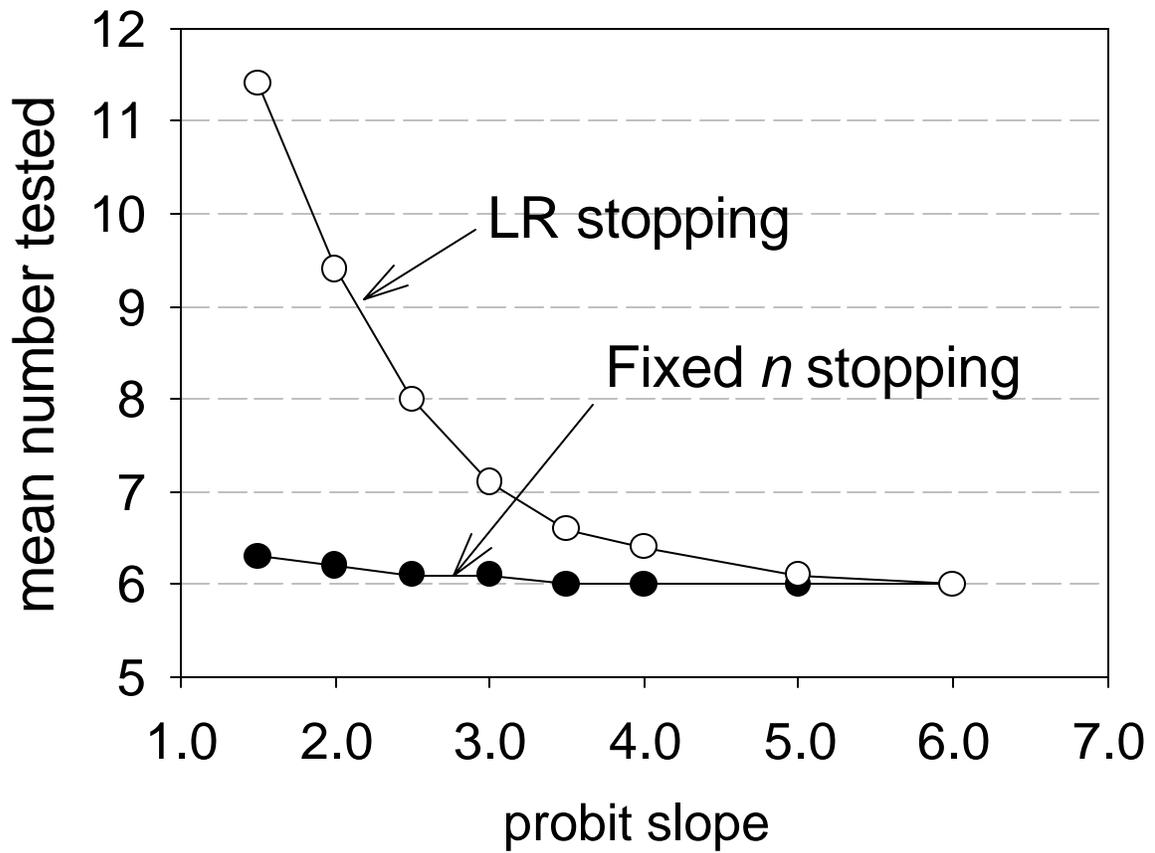
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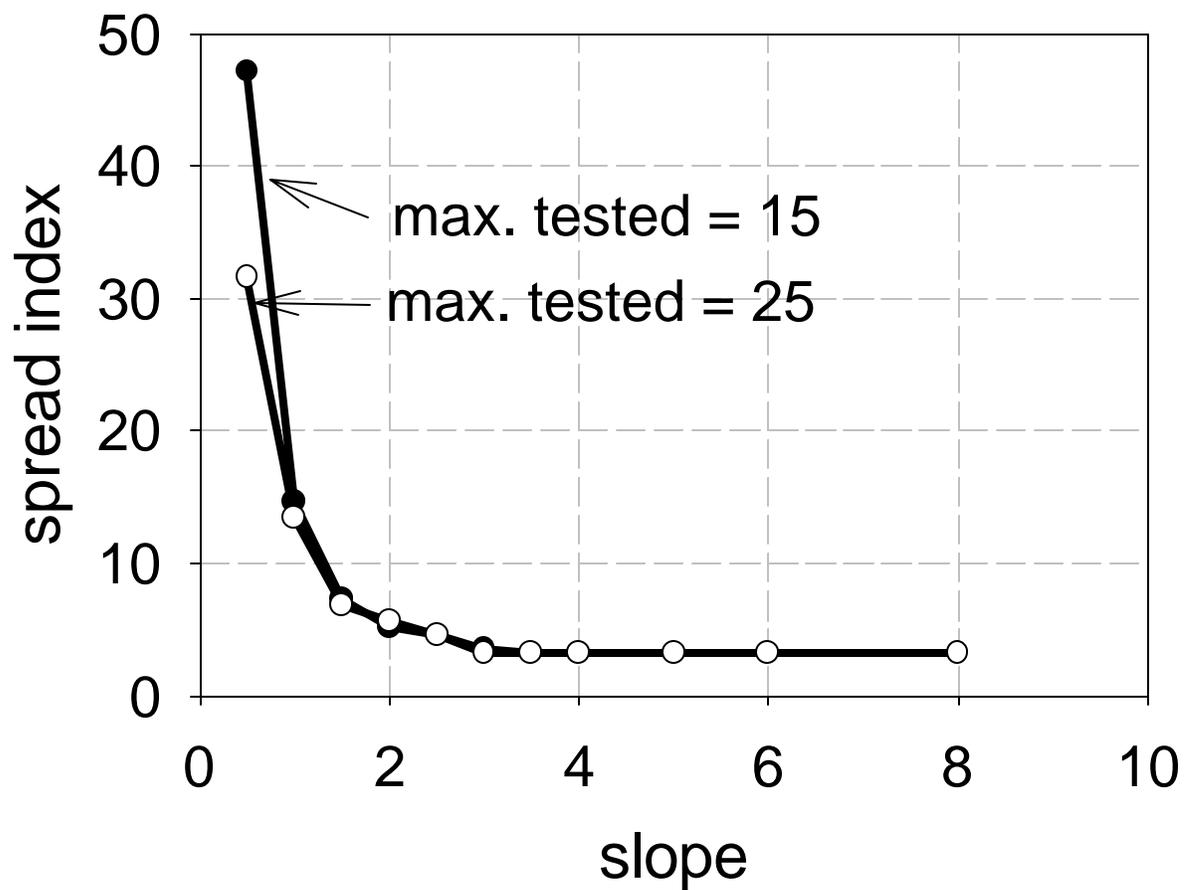
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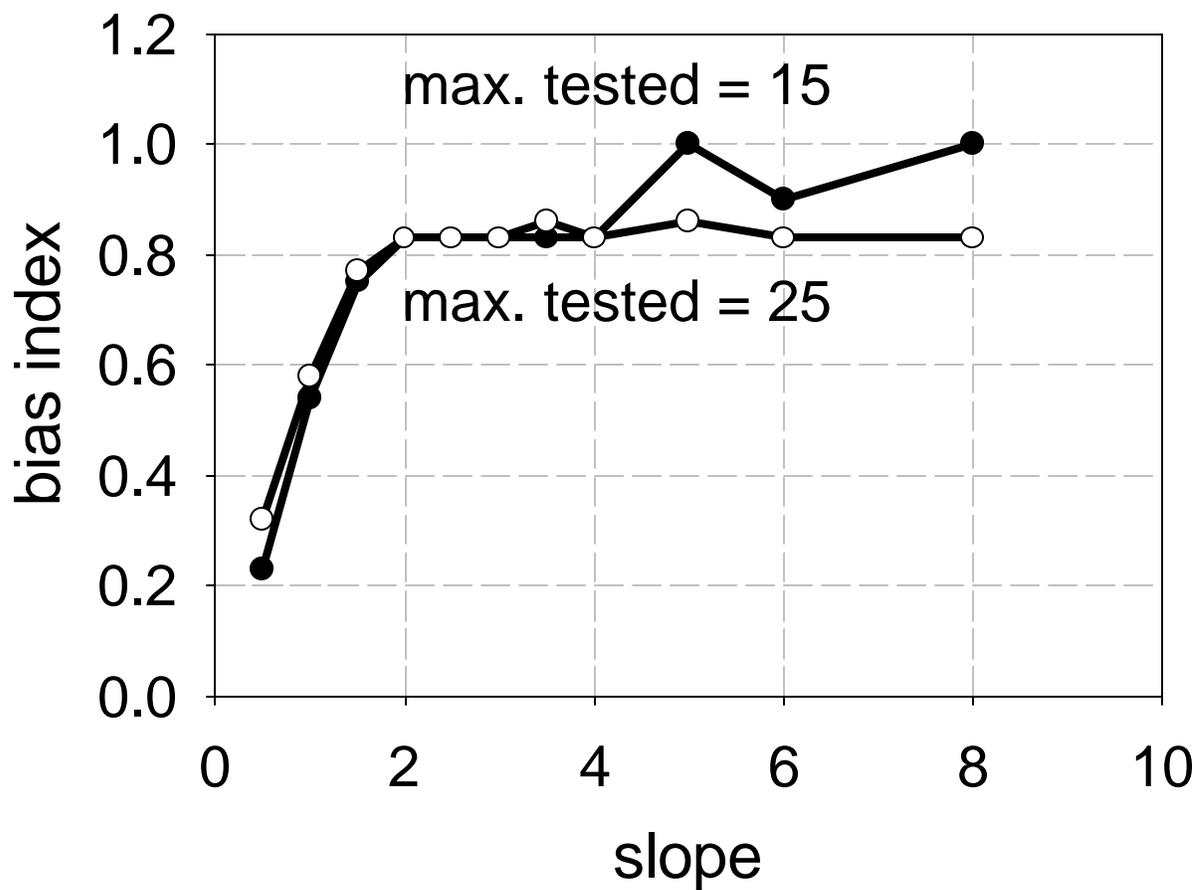
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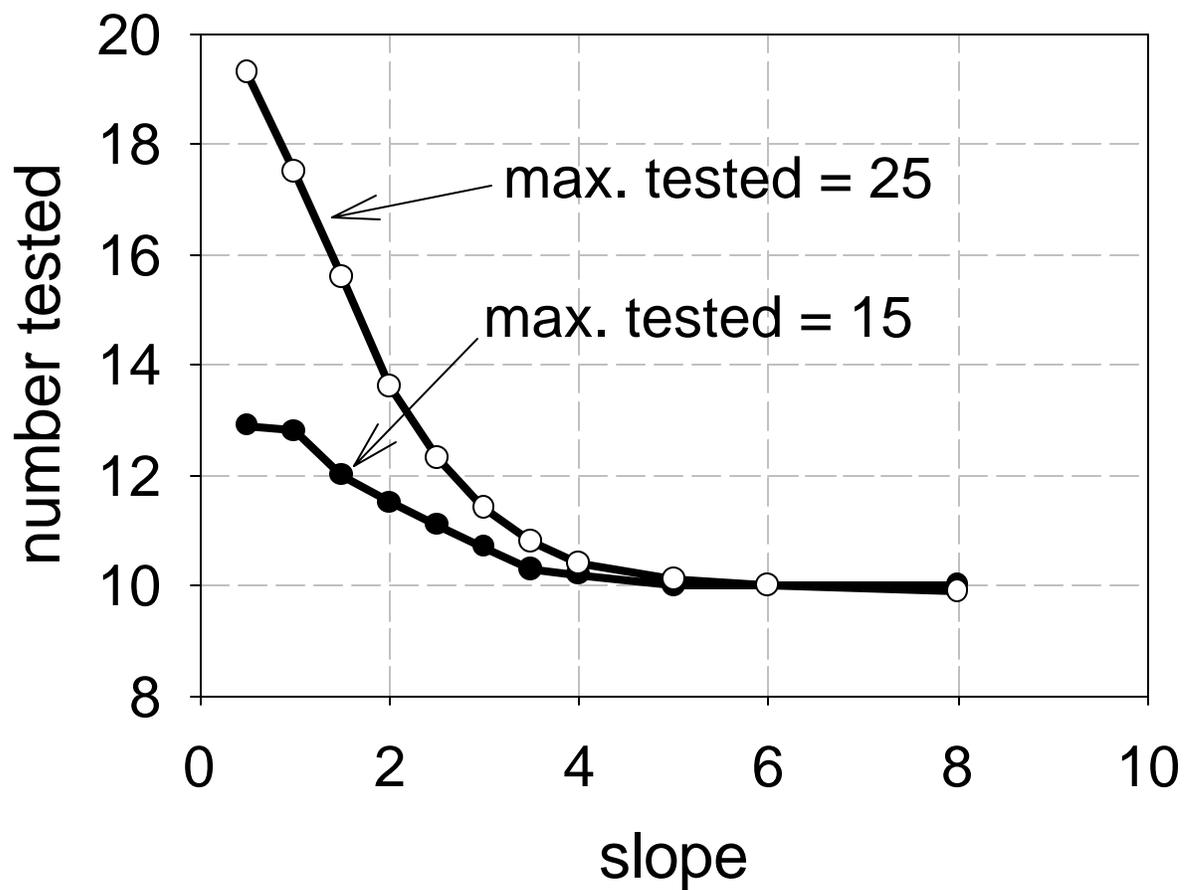
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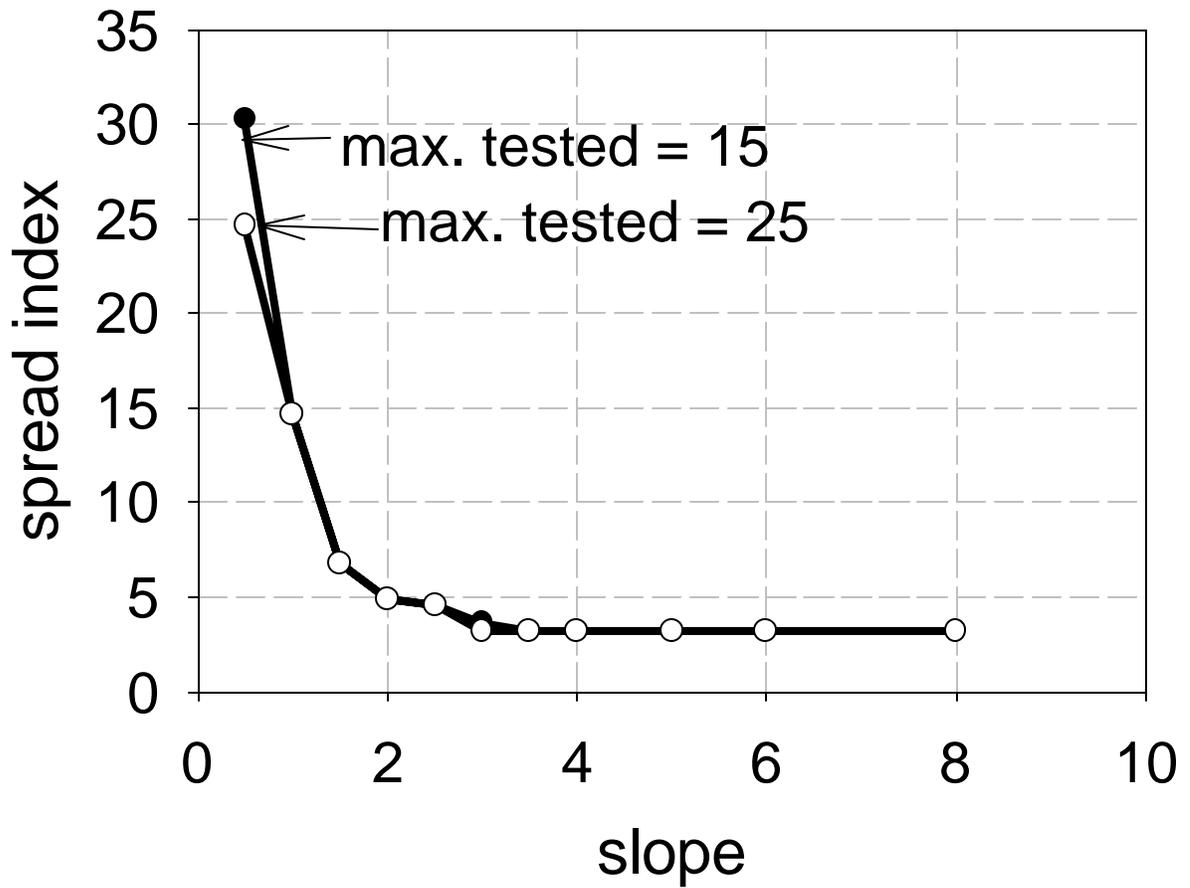
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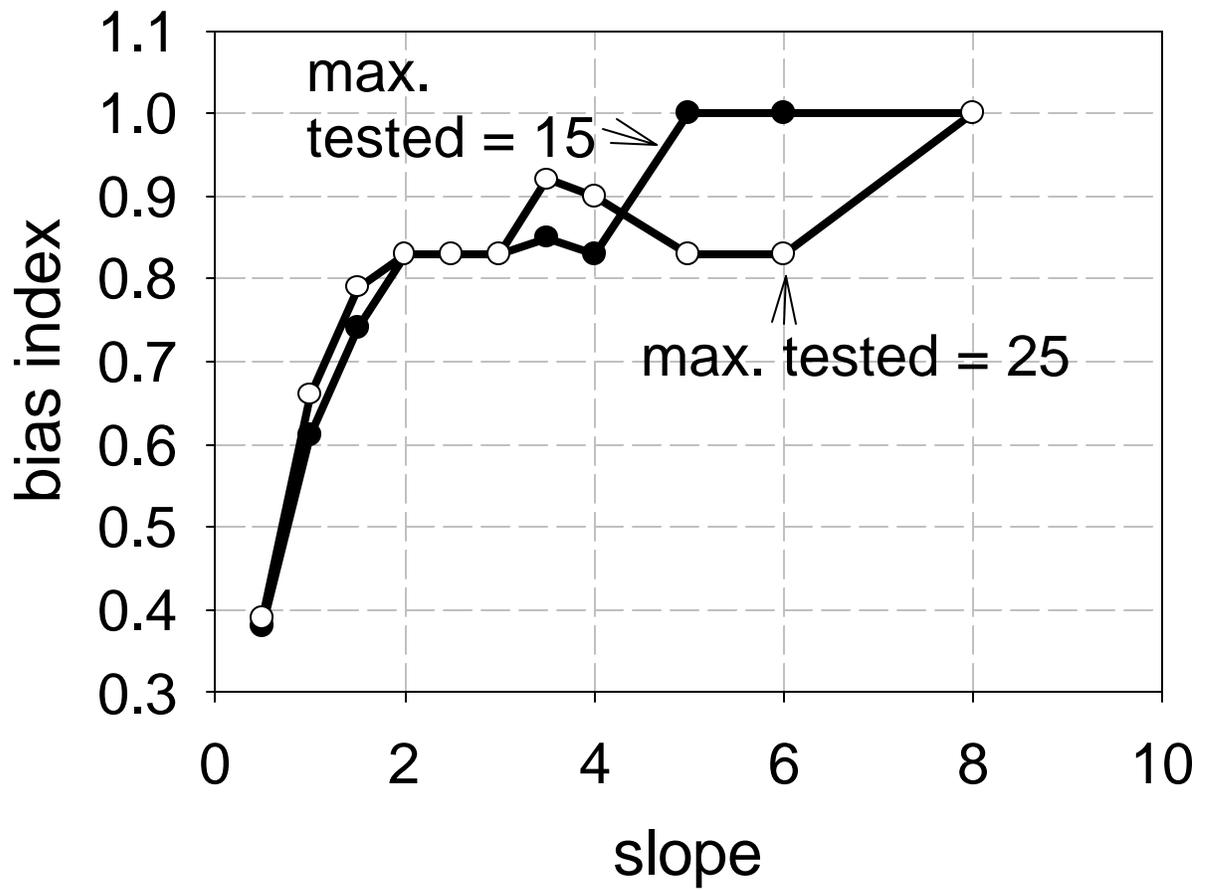
Initial Dose = LD50 / 100



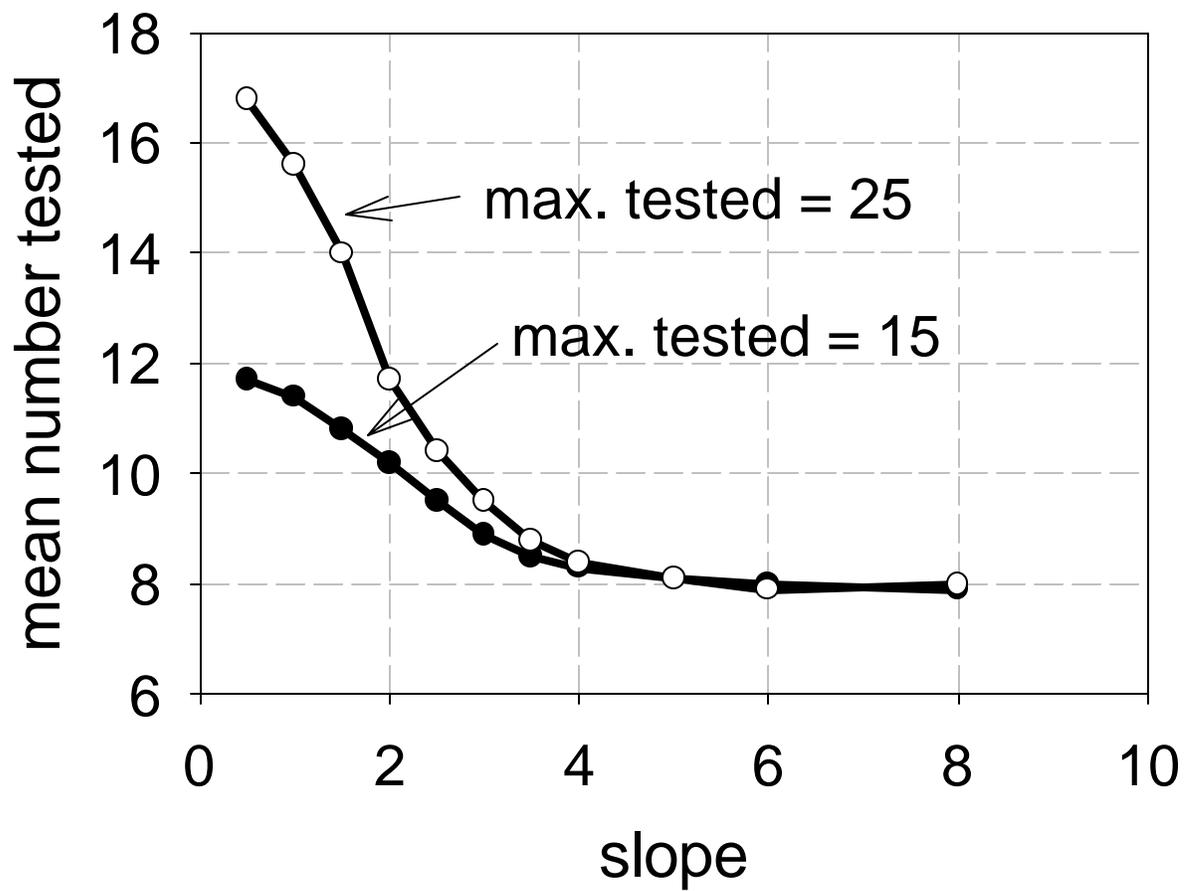
Initial Dose = LD50 / 10



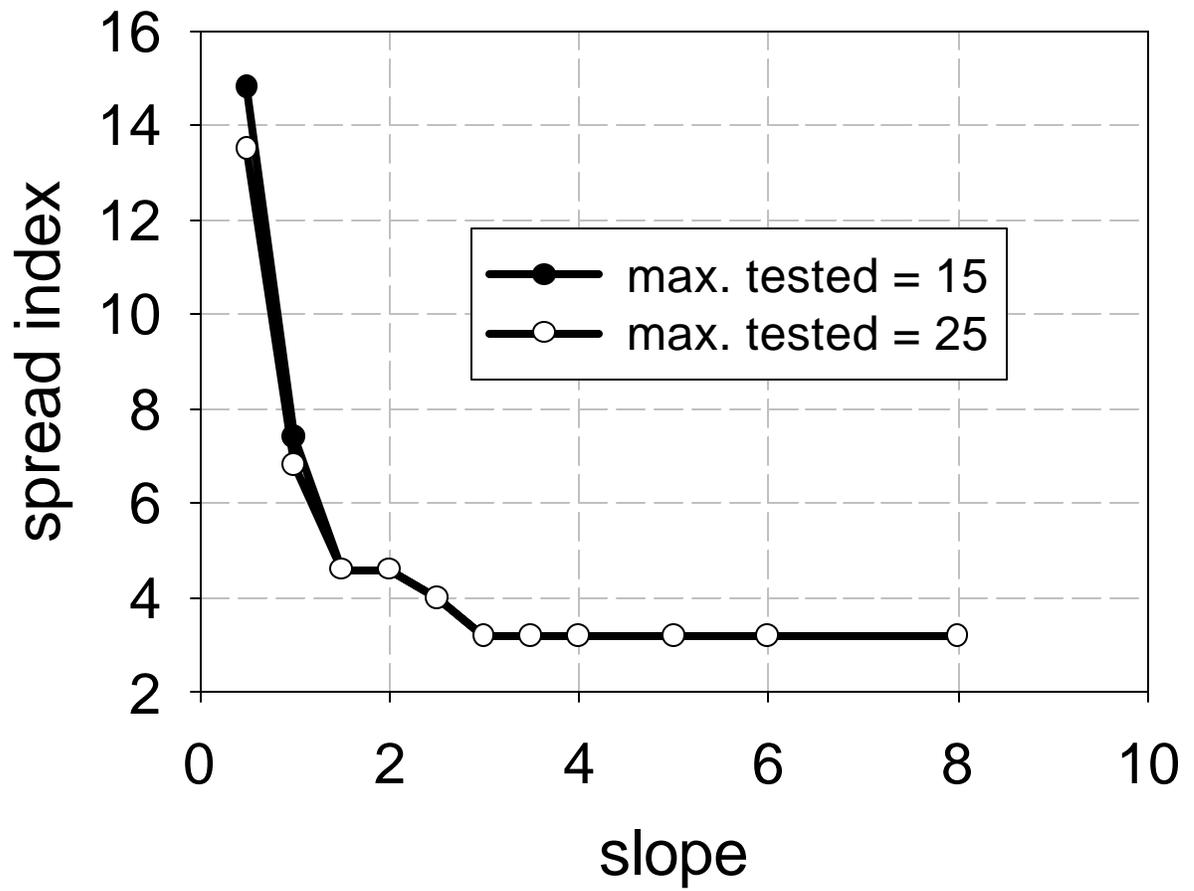
Initial Dose = LD50 / 10



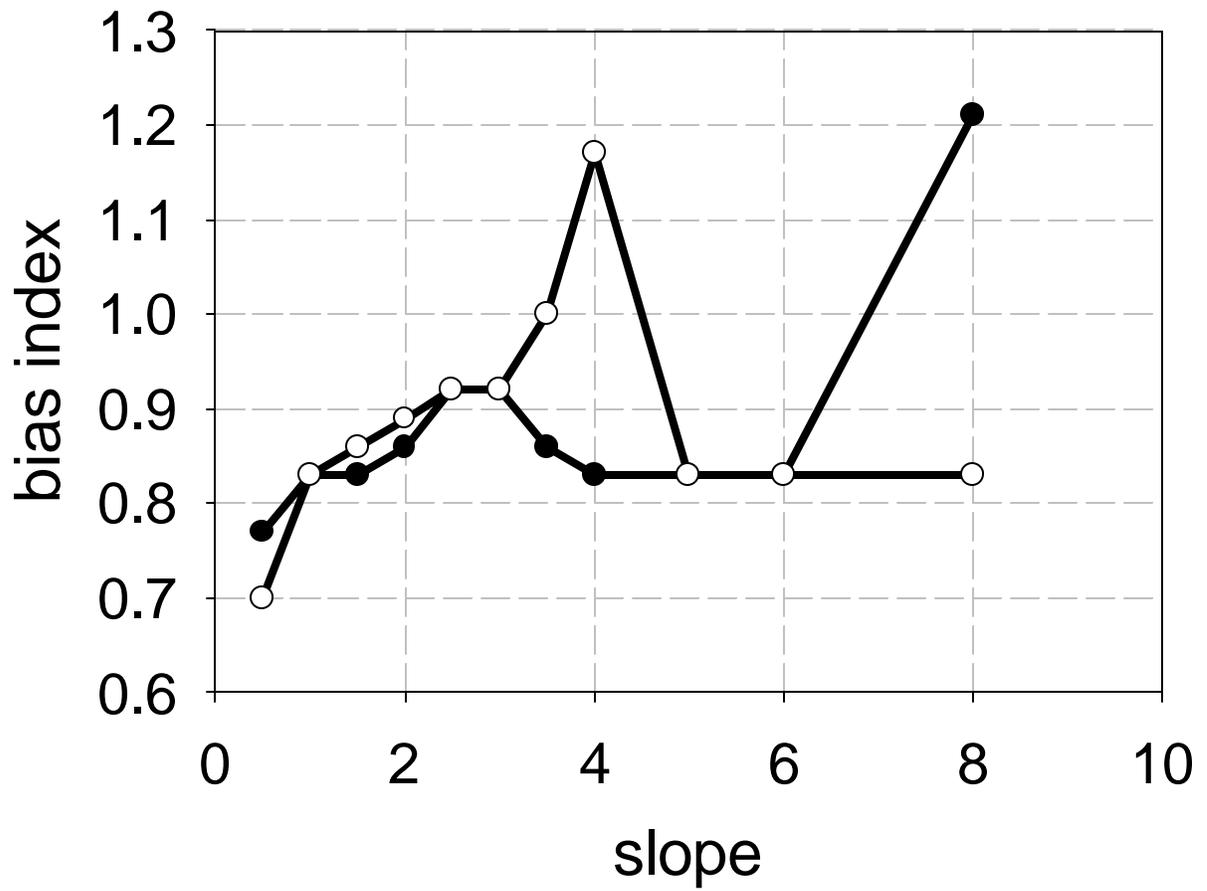
Initial Dose = LD50 / 10



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