Impact of dose-group allocation on TD50 reliability

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Abstract

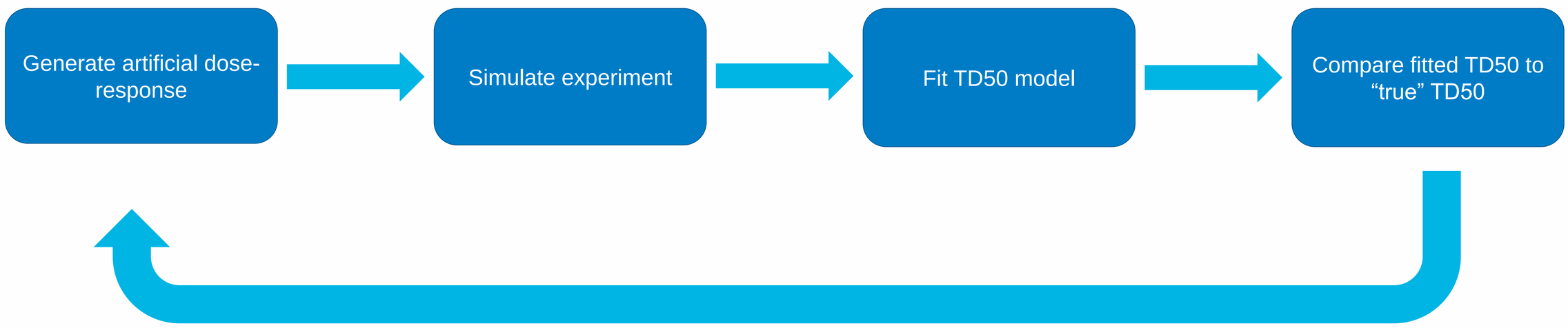
OECD guidelines provide a set of criteria by which to assess the reliability of a given carcinogenicity study. Unfortunately many tumorigenic dose 50s (TD50s) are based on historical studies which do not meet modern OECD guidelines, specifically recommendations on dose-group sizes (minimum 50 animals) and number of doses (3 dose-groups plus control) given in guideline 451. While TD50s can still be generated for these studies it is not clear whether they provide useful estimates. We simulate the effects of different dosing arrangements on the reliability of TD50 estimates and conclude that total number of animals and number of doses are the primary indicators of reliability. Studies with small (less than 50) dose-group sizes should still provide reliable estimates providing the total number of animals is sufficient.

Method

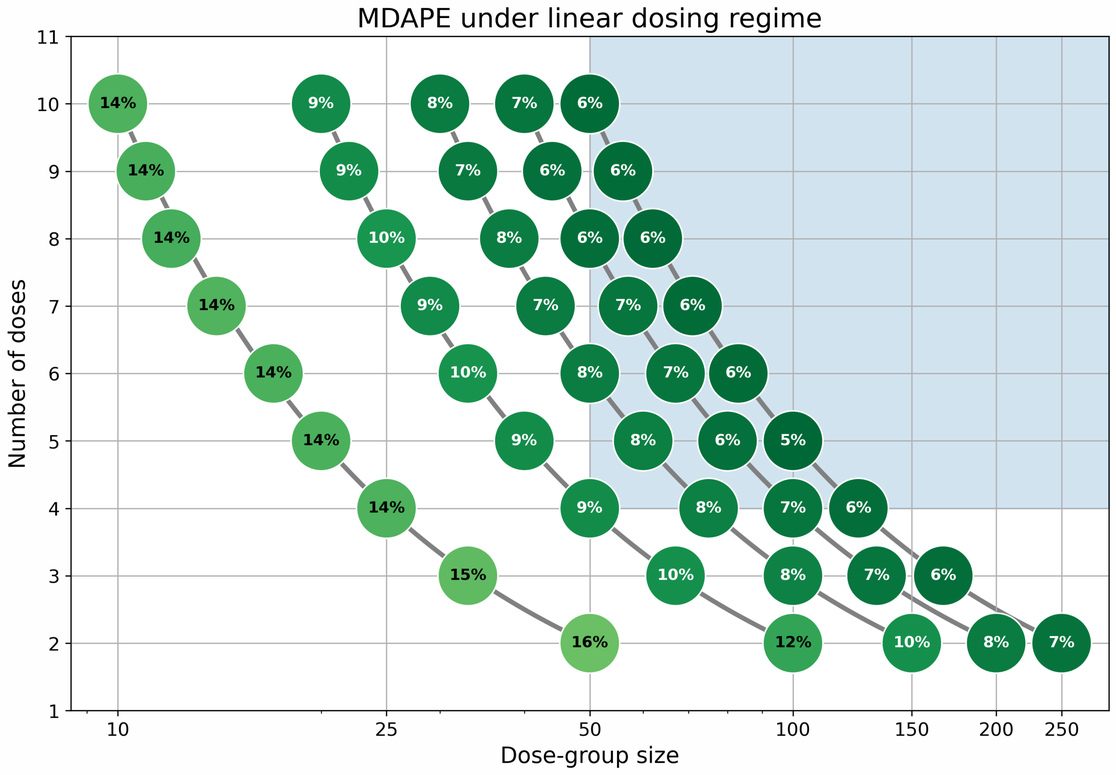
Simulations were performed by generating random dose-response relationships with known TD50s. These were then used to generate virtual experiments with different numbers of dose-groups and animals per group. The TD50 model was fitted to the virtual experiments and the predicted TD50 compared to the “true” TD50 for each experiment.

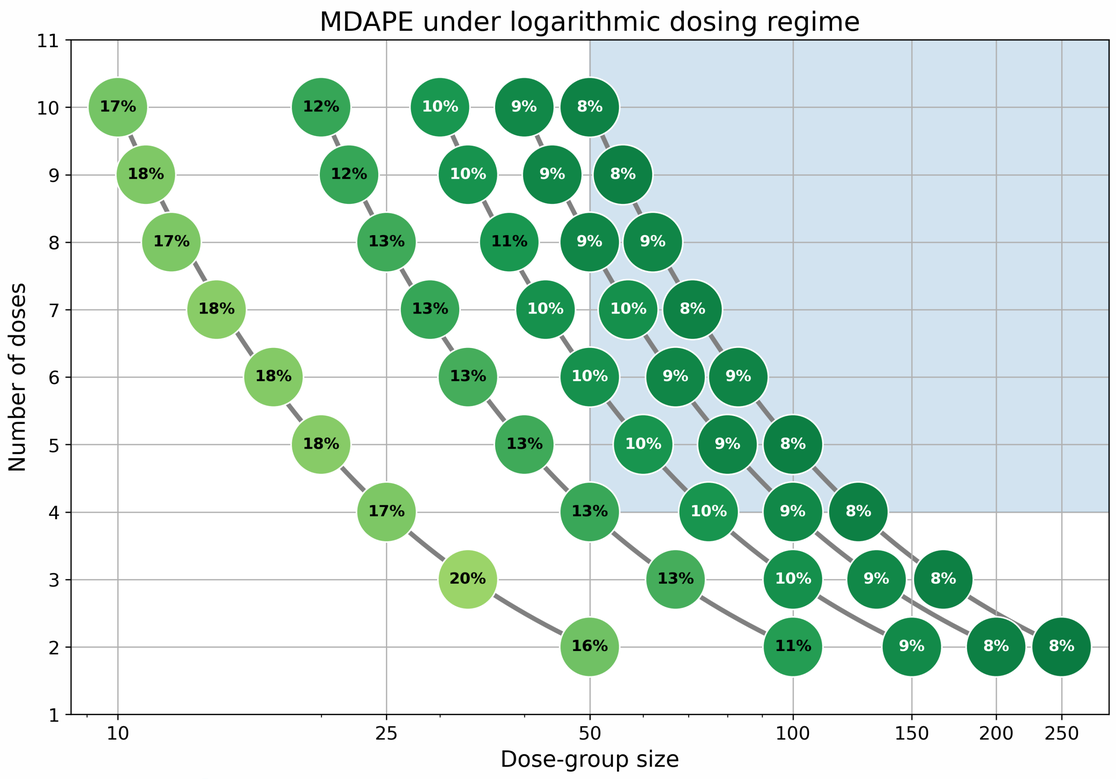
Different cases were investigated depending on response type (responses that match the TD50 model or random monotonic responses), and dose spacing (linearly or logarithmically spaced).

The median absolute percentage error (MDAPE) provides a robust way of assessing the impact of dose-group number/size on TD50 reliability.

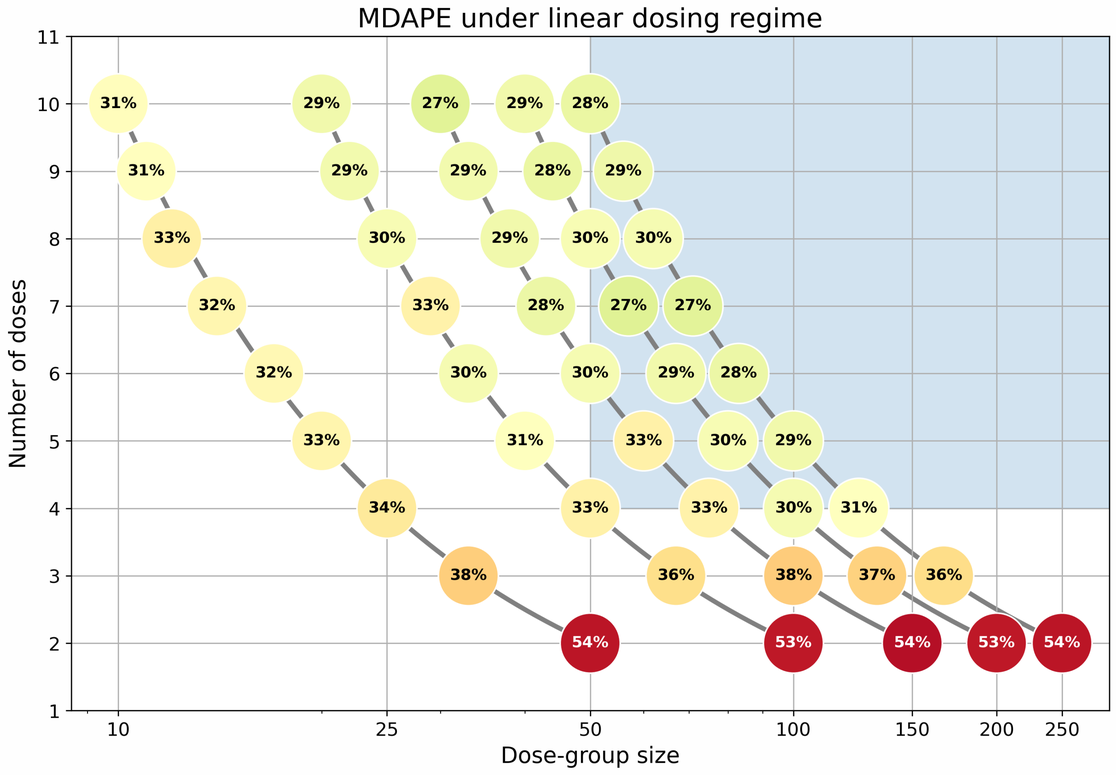


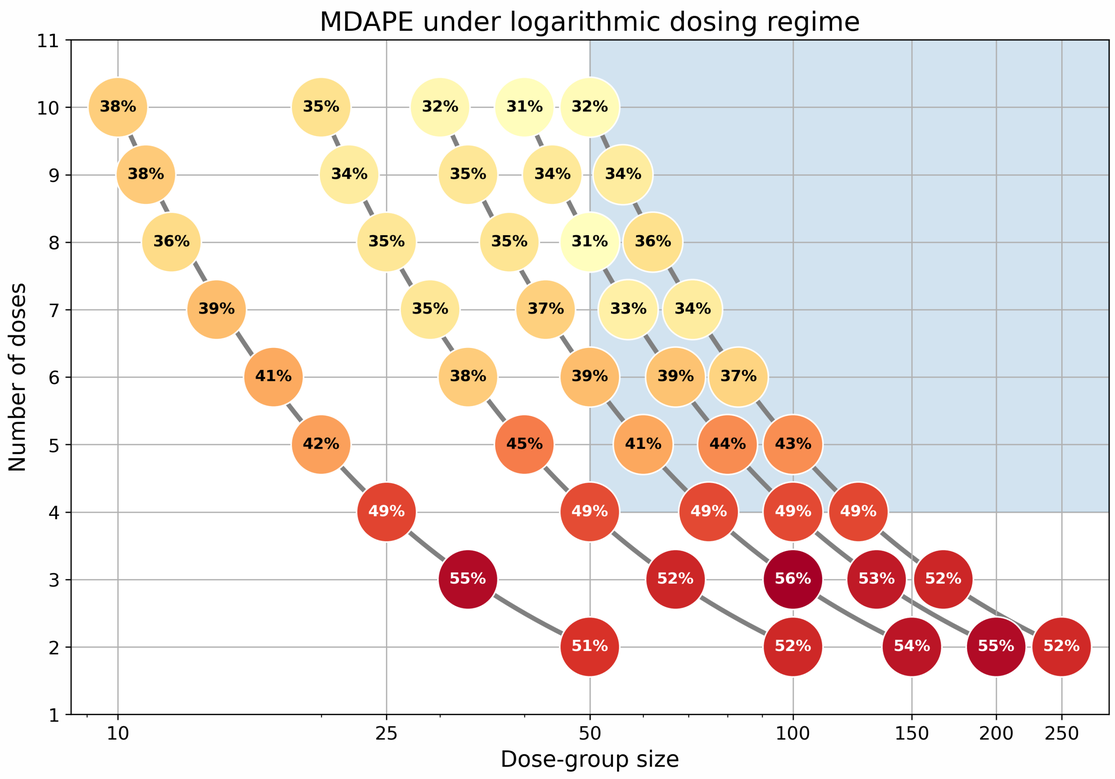
Expected TD50 response





Random dose-response





Conclusions

1. OECD guidelines (blue region) do a good job of excluding unreliable regions.
2. In the best case only the total number of animals matters.
3. In the worst case more doses with a smaller group size gives improved results.

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