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cc:
Subject: slope estimation procedure with parallel up-down sequences

In order for a procedure with parallel UD sequences to work for estimating the slope, I conjecture that it is best for the initial doses to be selected so that they have either high or low response probability, so that sequences with a nominal n of 2 will be likely to terminate in the tails of the tolerance distribution rather than close to the LD50. The procedure I simulated is carried out in stages, with parallel sequences of nominal n 2 in each stage. At each stage, initial test doses are chosen to equal either (1) the highest dose tested at all previous stages, such that there were no observed responses at that dose or at any lower tested doses; or (2) the lowest dose tested, such that there were always observed responses at that dose as well as at any higher tested doses.

Stage 1: Tier I procedure with proposed LR stopping rule;
Stage 2: Two sequences with step size 2 (log scale), one starting with the highest non-response dose, and one starting with the lowest all-response dose.
Stage 3: Two sequences with step size 0.5, ... [as for Stage 2]
Stage 4: Two sequences with step size 0.25, ... [as for Stage 2]
Stage 5: 3 sequences with step size 0.125, 2 starting from the highest non-response dose, and one starting from the lowest all-response dose.

In cases where the lowest tested dose had at least one response, the starting dose was chosen to be the lowest tested dose, divided by the progression factor. Similarly, in cases where the highest tested dose had no responses ... . Where these decisions would result in a value outside the range 1-5000 units, the initial test dose was chosen to equal the corresponding bound value (1 or 5000).

Following are features only used in Tier I and not for the additional Tier II sequences. No maximum number was used. No rule was used related to stopping at a bound value. Test doses close to but not exceeding a bound value were not set equal to the bound value. Otherwise, the restriction on the range of test doses was as we have discussed (the test doses can be constant at a bound value or move to the interior of the range).

(Based on 2000 simulated studies per scenario, LD50 = 250 units, initial test dose 25 units for the Tier I test.)

slope results

mea.num. slope	#fitted (%)	mean	5%	95%	F95/5	tested
2	1963. (98%)	2.6438	1.4314	4.8040	3.3562	40.
4	1674. (84%)	5.3881	2.7250	9.5593	3.5080	36.
8	1060. (53%)	8.1532	4.8074	12.941	2.6919	33.

* the number tested includes the number for Tier I;
* the probit model was fitted when there were at least 2 doses with partial mortality; also,
when their were exactly 2 with partial mortality, the higher dose was required to have higher mortality.
The slope was required to be positive.