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The development of response surface pathway design to reduce animal numbers in toxicity studies

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Background: This study describes the development of Response Surface Pathway (RSP) design, assesses its performance and effectiveness in estimating LD50, and compares RSP with Up and Down Procedures (UDPs) and Random Walk (RW) design.

Methods: A basic 4-level RSP design was used on 36 male ICR mice given intraperitoneal doses of Yessotoxin. Simulations were performed to optimise the design. A k-adjustment factor was introduced to ensure coverage of the dose window and calculate the dose steps. The performance of the RSP designs and a comparison of UDPs and RW were assessed by simulations. The optimised 4-level RSP design was used on 24 female NMRI mice given Azaspiracid-1 intraperitoneally.

Results: The *in vivo* experiment with basic 4-level RSP design estimated the LD50 of Yessotoxin to be 463 µg/kgBW. By inclusion of the k-adjustment factor with equal or increasing numbers of mice on increasing dose levels, the estimate changed to 481 µg/kgBW and 447 µg/kgBW, respectively. The optimised 4-level RSP estimated the LD50 to be 473 µg/kgBW. The simulations showed that the inclusion of the k-adjustment factor, reduction in sample size and incorporation of a multinomial outcome gave estimates of the LD50 that were as good as those with the basic RSP design. Simulated comparison of the RSP design with UDPs and RW design demonstrated the superiority of RSP.

Conclusion: Optimised RSP design reduces the number of animals needed. The design converges rapidly on the area of interest and is at least as efficient as both the UDPs and RW design.

Biography

Stig Larsen has completed his Dr. Sc in 1982 at Ullevål University Hospital, Oslo University. He has experience in both Pharmaceutical companies and CROs. He has 286 publications in international medical journals. From 1998, he has been Professor in Controlled Clinical Research Methodology and Statistics with 129 international publications in the field and keeps still this position. He has supervised more than 40 PhD fellows and has today 4 more in pipeline.

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