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PRESCRIPTION

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THE SIGNIFICANCE OF SIGHTING STUDIES AND LIMIT TESTS IN ANIMAL TOXICOLOGICAL STUDIES

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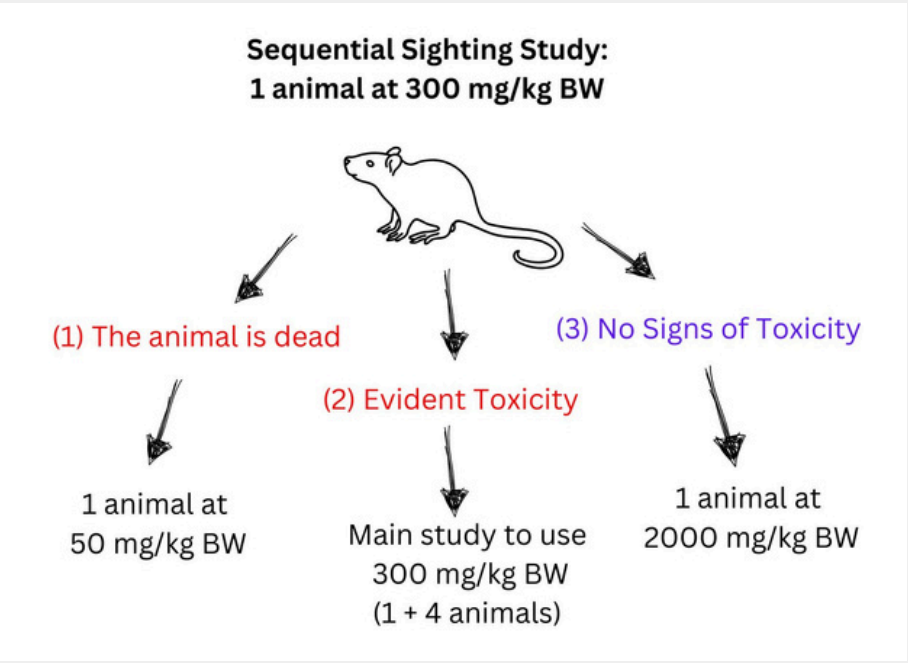
Toxicological studies on rats assess the potential toxicity of chemicals, pharmaceuticals, and other substances on living organisms. These studies are critical for determining a substance's toxicity profile, establishing safe exposure levels, and protecting human health and the environment. The Organisation for Economic Cooperation and Development (OECD) issues standardised guidelines for these studies to ensure consistency, reliability, and international acceptance of the findings.

IN THIS ISSUE



SIGHTING STUDIES are preliminary experiments that aim to determine the approximate range of doses or concentrations of a substance that could cause toxic effects. The initial dose for the sighting study is chosen sequentially from the fixed dose levels of 5, 50, 300, and 2000 mg/kg as a dose expected to produce obvious toxicity based on evidence from in vivo and in vitro data from the same chemical or structurally related chemicals. In the absence of this information, the initial dose will be 300 mg/kg (OECD420). Individual animals are observed for signs of toxicity after dosing at least once within the first 30 minutes, periodically within the first 24 hours, and daily thereafter for a total of 14 days. Tremors, convulsions, salivation, diarrhoea, lethargy, sleep, and coma should all be monitored. Animals found to be moribund, as well as those in severe pain or showing signs of distress, should be killed humanely. These studies aid in determining the appropriate dose levels for subsequent studies on acute, subacute, subchronic, and chronic toxicity. Also, it helps avoid the use of excessively high or unnecessarily low doses in main studies, thereby optimising the use of resources (e.g., animals, time, and materials).

LIMIT TESTS, on the other hand, are used to determine whether a substance is toxic at a predetermined dose level, which is typically set high to represent the worst-case scenario. If no toxicity is detected at this dose, additional testing at higher doses may be unnecessary. In a subacute oral toxicity study in rodents, if a test at one dose level of at least 1000 mg/kg body weight/day shows no observable toxic effects, a full study with three dose levels may not be required (OECD407). Limit tests can save time and resources by quickly determining whether a substance is unlikely to be toxic at the tested dose level. This data can help determine whether to conduct additional subchronic and chronic toxicity assessments. If toxicity is observed, it may be concluded that the study should be discontinued early in development, resulting in a no-go decision for the clinical trial.

To summarise, sighting studies and limit tests are critical to the design and implementation of toxicological studies. By refining the dose levels and reducing unnecessary exposure to high doses, they ensure that the studies are carried out efficiently, in accordance with the 3R principles (Replacement, Reduction, and Refinement), in compliance with regulatory requirements, and ultimately contribute to the safety assessment of substances.

FAQs:

1. What is the reason for conducting toxicological studies on rats?

- *To evaluate the toxicity of chemicals, pharmaceuticals, and other substances to living organisms.*
- *To determine the substance's toxicity profile, to establish safe exposure levels, and to protect human health and the environment.*

2. How does a sighting study help in optimising the use of research resources?

- It helps in determining the appropriate dose levels for the main studies by avoiding the use of excessively high or unnecessarily low doses.

3. What is the implication of the limit test in toxicological studies?

- Limit tests can quickly determine whether a substance is unlikely to be toxic at the tested dose level.
- The researchers can then proceed to the next level of toxicity testing (subchronic and chronic tests).

ABOUT THE MAIN AUTHOR

Dr. John Shia Kwong Siew is an Associate Professor in Clinical Pharmacy and Pharmacy Practice at Universiti Teknologi MARA (UiTM). With a diverse academic background, he first earned his Doctor of Veterinary Medicine degree in 2002, before pursuing a Ph.D. in Molecular Biology, which he completed in 2009. In addition to his roles in teaching and research, Dr. Shia Kwong Siew is currently serving as the President of the Laboratory Animal Science Association of Malaysia. He is also the Coordinator of the Laboratory Animal Facility and Management Unit at UiTM, where he contributes significantly to the advancement of laboratory animal science and welfare.