

## When and How to Demonstrate Safety and Toxicity of Potential Sterilants – Khan

Traditional neutering of companion animals, including dogs and cats, has been through surgical methods such as ovariectomy and orchidectomy. While surgical methods are useful in some situations, not all pet owners prefer these methods of controlling reproduction in their animals. Surgical methods have limited applications in controlling pet population since they require general anesthesia and post-operative care, and carry risk of infection and other surgery-related complications. Compassion, unnecessary procedure, cost, and behavior changes are some of the reasons cited by pet owners against using surgical methods for sterilization.

Currently, several non-surgical methods of sterilization are being investigated to control population in companion and wild animals. An ideal sterilant would be efficacious and could cause long-term infertility in both dogs and cats, males and females, and would be easy to administer, have fewer adverse effects, and be relatively safe and affordable. Some of the currently available methods of pharmacologic sterilization include hormonal treatment; immunocontraception; intratesticular, intraepididymal and intra vas deferens injections; and some other methods (intravaginal spermicides, mechanical barriers, intrauterine devices, cytotoxin conjugates). While pharmacologic methods of controlling reproduction are useful, there are several concerns. Immunocontraception methods seem to vary in effectiveness and duration. Long-term efficacy and possible adverse vaccine reactions are another disadvantage. Injection of steroid hormones does not consistently result in sterility. Various chemicals injected intratesticularly can cause local pain and inflammation. It is clear from the preceding discussion that long-term safety and efficacy of pharmacologic sterilants/compounds in dogs and cats have not been established.

The information provided here discusses general toxicity and safety guidelines employed for testing a potential pharmaceutical compound, including a sterilant for dogs or cats. The extent to which safety and toxicity of a compound is studied is largely dependent on its intended use. Toxicologic testing means that a compound is subjected through a series of short-term testing designed to detect a specific type of toxicity. The objective is to evaluate the relative potential of a compound for producing harm to biological tissues. There are no set toxicology tests every compound has to go through. The need for toxicological studies for a pharmaceutical compound intended for short periods (a few doses) is different than that for drugs which will be used for long periods of time. Generally, toxicological tests fall into three major categories primarily dependent upon the duration of tests. These tests are acute tests, prolonged or subchronic toxicity tests and chronic tests.

In general, acute tests involve administration of a test chemical on one occasion. The LD50 and other acute toxic effects are determined after one or more routes of administration in one or more species. Studies are performed in both adult male and female animals. Acute toxicity tests help determine a quantitative estimate of acute toxicity for comparison with other substances. It also provides information on target organ and clinical manifestations, establishes reversibility, and provides dose-ranging guidance for other studies.

Sometimes, subacute (repeated dose) studies are also performed to obtain information to establish doses for chronic studies later. Typically, three to four doses are used. Subchronic studies can last for different periods, but 90 days is the most common duration. These studies are usually conducted in two species by the route of intended exposure using two or three doses. The main goal from these studies is to establish no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). For pharmaceutical agents to be registered with the FDA, acute and subchronic or other additional tests are required before filing application for an investigational new drug (IND). Clinical trials can commence at this stage if IND has been approved.

Chronic or long-term studies are performed similar to subchronic studies, except that the duration of exposure is longer than 3 months (for 6 months to 2 years in rodents, 5-7 years in dogs). It helps demonstrate absence of toxicity when the doses involved represent some practical concentration. Chronic studies can help assess the cumulative toxicity and carcinogenic potential of a chemical.

In addition to information obtained from acute and prolonged toxicology tests, other information such as physicochemical properties (structure activity relationship, solubility, stability) of a chemical or similar other compounds, teratogenicity, carcinogenicity, and mutagenicity potential, pharmacokinetic or toxicokinetics information (absorption, distribution, metabolism, elimination, mechanism of action) skin, behavioral, and immune effects, species differences, individual differences in response, therapeutic index, margin of safety, drug interaction, environmental fate (biodegradation), analytical method for quantitative estimation of the chemical or its metabolites in environmental or biological samples, risk of secondary toxicity (humans or other animals), mechanisms to monitor and document adverse effects, and availability of treatment information can further help determine safety and toxicity of a chemical.