

LOAEL—Lowest Adverse Effect Level: The lowest exposure level at which there are statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed vs. control populations.

MTD—Maximal Tolerated Dose or Minimally Tolerated Dose, depending on the implication. This is the dose at which biologically significant effects, directly/indirectly due to test compound administration, are found to have an appreciable effect on the quality and length of the lifespan of the animal. This may include a variety of outcomes, such as a lack of feed intake due to unpalatability of the test article, direct effect on the cardiovascular system, cecal dilatation and torsion due to changes in cecal flora in rodents.

Within this framework, an adverse effect is a biochemical, morphological, or physiological change that contributes to or is responsible for adversely affecting the performance (e.g., lifespan, health, well-being, growth) of the organism. Alternatively, it may reflect a reduced ability of the organism to respond to its environment. A biologically significant effect is a response that is considered to have a substantial or noteworthy positive or negative effect on the well being of the biological system. This is contrasted with a statistically significant effect that may not be meaningful to the state of health of the organism (3).

Some adverse reactions are also reflective of physiologic idiosyncrasies associated with a particular species. These do not correlate with exposure–response relationships in humans. Several of these peculiarities are summarized in [Table 1](#) (4).

In some cases, biological effects may reflect adaptive responses that are not related to the inherent toxicity of the test substance itself. An example of such a response is the histological change that may occur as an adaptive reaction to the inhalation of a compound (5). These include: mucus cell hyperplasia induced by dehydration of the nasal epithelium due to inhalation of aerosols; macrophage accumulation in the lung after exposure to low-solubility materials (in the absence of any other signs of an inflammatory reaction); and replacement of alveolar epithelium by ciliated epithelial cells as an adaptive response to high concentrations of exogenous materials.

Despite our best efforts, there will continue to be cases where toxicity in man could not be predicted from animal data. For example, fencloriz acid, which was a potential anti-inflammatory compound, was found to be without any adverse effects in an array of animal species including mouse, rat, dog, rhesus monkey, patas monkey, rabbit, guinea pig, ferret, cat, pig, cow, and horse. However, it caused acute cholestatic jaundice in people (6).