The No-Observed-Adverse-Effect-Level (NOAEL) in Drug Safety Evaluations

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Summary
The NOAEL is an important part of the non-clinical risk assessment. It is a professional opinion based on the design of the study, indication of the drug, expected pharmacology, and spectrum of off-target effects. The definition of NOAEL, in regulatory guidance documents and in the general scientific literature, varies. This is based, in part, on the varied definitions of what constitutes an adverse effect. Toxicologists, either investigating or reviewing, have not been consistent in defining an effect as either adverse or acceptable. The common definition of NOAEL, "the highest experimental point that is without adverse effect" serves us well in general discussions. It does not, however, address the interpretation of risk based on toxicologically relevant effects, nor does it consider the progression of effect with respect to duration and/or dose. It is recommended that, for pharmaceutical development, the common definition of NOAEL be replaced with the following functional definition: "the highest dose/exposure that does not cause biologically important (toxicologically relevant) increases in the frequency or severity of effects between the exposed population and the appropriate control. While minimal toxic effects may be observed at this level, they are not considered to endanger human health, or be precursors of serious events". It must be remembered that the NOAEL is not risk free, and that the development of pharmaceuticals requires an assessment of the risk/benefit relationship. This paper will discuss the application of a functional definition of the NOAEL in toxicology evaluations.